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Vision, Attention and Action in Posterior Cortical Atrophy and other Dementias.

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Abstract

Posterior Cortical Atrophy (PCA) is a rare, progressive dementia characterised by visuospatial and visuoperceptual deficits (often with intact visual acuity), and a generally younger age of onset than typical Alzheimer's disease (AD) (Aresi & Giovagnoli, 2009; Caixeta, Taleb, Ghini, Dias Soares, de Melo Caizera & Vargas, 2013; Mendez, Ghjarania & Perryman, 2002). Patients with PCA typically present with fewer memory deficits, better verbal fluency, and better insight into their diagnosis compared with typical AD, although PCA and AD tend to converge clinically at advanced stages of disease progression (Lehmann et al., 2012). Despite being identified by Benson and colleagues three decades ago, there are still no widely agreed clinical diagnostic criteria for PCA and it remains relatively poorly understood (Benson, Davis & Snyder, 1988; Crutch et al., 2017).

This PhD study was comprised of two phases. The initial screening phase involved a diverse battery of assessments with two main aims. First, this battery was intended to investigate the sensitivity and specificity of different screening tests in discriminating PCA patients (n = 6) from patients with other neurodegenerative dementias (n = 21) (typical Alzheimer's disease, frontotemporal dementia, Lewy body dementia, corticobasal degeneration, and primary progressive aphasia). The Modified Luria Alternating Square and Triangles (M-LAST) task achieved the highest sensitivity and specificity, closely followed by target cancellation and bisection tasks. The M-LAST task has not been reported previously in the assessment of PCA patients, but may have considerable potential for use in diagnostic settings. Similarly, an unusual variant of the bisection task (gap bisection, McIntosh et al., 2004) yielded the most impressive sensitivity for PCA. The secondary aim of the screening phase was to identify whether patients with other neurodegenerative diseases demonstrated deficits on the assessments which were specific to early visual function, as this is an area that has not been addressed previously in the literature. There was evidence of significant impairment for patients other than

PCA on a number of measures. However, the most striking results from patients with dementias other than PCA were obtained on the second phase of assessment.

The second laboratory-based phase aimed to more fully characterise the visuoattentional deficits associated with PCA (n = 5) and other dementias (n = 13), through the use of eye-tracking and motion-tracking technology. The PCA patients proved difficult to test under these conditions, as their visual impairments were so advanced and generalised that they appeared almost functionally blind on some tests. The most exciting novel results were obtained from patients with AD, in whom evidence of optic ataxia (misreaching to peripheral targets) was found for three of the four AD patients tested on a pointing task. These results, discussed in context with other recently published evidence (Gordon et al., 2018), suggest that screening for optic ataxia may have potential as a behavioural symptom potentially sensitive to early neuronal changes associated with AD.

A systematic review of the literature was conducted in order to investigate the use of visual attention or visuomotor-specific assessments in the evaluation of patients with PCA. A case study was conducted of visual form agnosic patient DF, in whom recent evidence of optic ataxia has been found (Rossit et al., 2018; Hesse, Ball & Schenk, 2012, 2014). Strong evidence of optic ataxic-like pointing errors was observed in patient DF, with preserved grip scaling, implicit avoidance of obstacles and perceptual matching. An additional study on healthy participants was conducted in order to test whether attentional demands modulate performance on a visuomotor pointing task. The results indicated that increasing attentional demands led to optic ataxic-like pointing errors, thus the experimental manipulation appeared to serve as a model of optic ataxia in the healthy brain.

Lay Summary

Posterior Cortical Atrophy (PCA) is a rare 'visual' form of dementia. Typically, PCA affects people of a younger age than those with typical Alzheimer's disease (AD). Patients with PCA also generally have better memory and language abilities than those with AD, and are more aware of their diagnosis. However, differences between AD and PCA tend to lessen as the disease progresses in PCA, with PCA and AD patients showing similar symptoms at later stages. Although PCA was identified around 30 years ago, it is still quite a poorly understood form of dementia. Work is still on-going to create a clear set of diagnostic criteria for the disease. This research project investigated some of the vision and movement problems associated with PCA and compared patients with PCA to patients with other neurodegenerative diseases.

The study was split into two main phases. The first phase involved testing patients on a range of tests designed to challenge their vision and attentional abilities. The aims of this phase were to see how effective the included tests were at identifying problems specific to PCA. The results indicated that the best test to discriminate PCA from non-PCA patients was a drawing/copying task, which is not currently used by doctors to test for PCA-like symptoms. This test could become a useful method to test future patients for PCA-like symptoms. The results also found that non-PCA patients also show some vision and attention problems. The second phase of testing explored these in greater detail.

The second phase of testing involved patients being tested in a specialised laboratory using eye- and hand-tracking technology. The tests in this phase were designed to give much more detailed information on the patients' abilities. Unfortunately, the PCA patients proved very hard to test under these conditions, as their visual problems were generally so severe that they found it very hard to perform the tests at all. The most interesting results came from testing patients with Alzheimer's disease (AD). Specifically, evidence for a problem reaching accurately to objects in side-vision was found. These sorts of problems are

already known to be associated with damage to a brain area called the precuneus. This brain region has recently been shown to be one of the first areas in which brain changes associated with the onset of AD happen (Gordon et al., 2018). Finding evidence of such problems in the AD patients in this study is interesting because it suggests that this kind of testing could become a useful way to detect AD, possibly even before other symptoms, like memory and language problems, develop.

The thesis also includes a review of all the previous research on PCA, as well as a study of action abilities in a non-dementia patient with known damage to the back of the brain. Lastly, a test was done on healthy people to see if distracting them with a hard task at the same time as asking them to point to objects in their side-vision would lead to similar patterns of mistakes as were seen in the patients.

Declaration

I declare that this thesis has been composed solely by myself and that it has not been submitted, in whole or in part, in any previous application for a degree. Except where stated otherwise by reference or acknowledgment, the work presented is entirely my own.

I confirm that this thesis presented for the degree of PhD in Psychology (Clinical Neuropsychology), has

i) been composed entirely by myself
ii) been solely the result of my own work
iii) not been submitted for any other degree or professional qualification

I declare that this thesis was composed by myself, that the work contained herein is my own except where explicitly stated otherwise in the text, and that this work has not been submitted for any other degree or professional qualification except as specified.

Harriet E. Ingle
15th August 2018

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Index of Acronyms

ACE-III	Addenbrooke's Cognitive Examination – Third Edition
AD	Alzheimer's Disease
ANOVA	Analysis of Variance
ARC	The Anne Rowling Regenerative Neurology Clinic
AvB	Avoidance bias
AvS	Avoidance sum
Aβ	Beta-amyloid peptide [plaques]
BORB	Birmingham Object Recognition Battery
CBD	Corticobasal Degeneration
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CFX	Cueing effect
CIB	Closing-in behaviour
CJD	Creutzfeldt-Jakob disease
CoL	Cost of Local
CoO	Cost of Overlapping
CoP	Cost of Pairs
COP	Contralateral obstacle position
CoR	Cost of Relief
COW	Contralateral obstacle weighting
CSF	Cerebrospinal fluid
CT	Computerised tomography
DART	Edinburgh Cognitive Diagnosis, Audit, Research and Treatment Register
DBE	Directional bisection error
DLB	Dementia with Lewy Bodies
DPL	Change in response position given the leftmost part of the line
DPR	Change in response position given the rightmost part of the line
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
EOAD	Early onset Alzheimer's disease
EWB	Endpoint weightings bias
EWS	Endpoint weightings sum
FDR	False Discovery Rate
FEF	Frontal eye fields
FTD	Frontotemporal Dementia
GP	General Practitioner
IAA	Inhibition of attentional allocation model
IOP	Ipsilateral obstacle position
IOW	Ipsilateral obstacle weighting
IPS	Intraparietal sulcus
LBD	Lewy-Body Dementia
MAP	Maximum aperture
MCI	Mild cognitive impairment
MD	Mixed dementia
MeSH	Medical subject headings (from PubMed)

MGA	Maximum grip aperture
M-LAST	Modified Luria Alternating Square and Triangles Test
MRI	Magnetic resonance imaging
NDD	Neurodegenerative disease
NFTs	Tau neurofibrillary tangles
NICE/SCIE	National Institute for Health and Clinical Excellence / Social Care Institute for Excellence
NOI	Notification of Interest
OA	Optic ataxia
OA	Ocular apraxia
OSQAT	Observational study quality assessment tool
PCA	Posterior Cortical Atrophy
PDD	Parkinson's disease dementia
PET	Positron emission tomography
PI	Primary Investigator
PPC	Posterior parietal cortex
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
P-τ	Hyperphosphorylated tau
RT	Reaction time
SA	Simultanagnosia
SfA	Selection-for-action
SfP	Selection-for-perception
SPECT	Single-photon emission computerized tomography
SPL	Superior parietal lobule
SWM	Spatial working memory
TCDT	The Clock-Drawing Test
TEA	Test of Everyday Attention
TROG	Test for Reception of Grammar – I
TVA	The Theory of Visual Attention
VA	Visual agnosia
VaD	Vascular dementia
VAM	Visual Attention Model
VCA	Visuo-constructional apraxia
τ	Tau

Index of Symptoms, Concepts, and Terms

Acalculia	An acquired disorder, manifesting as an inability to perform calculations.
Action-intentional spatial bias	An asymmetry in the motor-intentional 'aiming' system, manifesting as a a deficit in (or an inability to execute) purposeful movement towards one side of space.
Agraphia	An acquired constructional disorder, manifesting as an inability to write.
Alexia	An acquired reading disorder, manifesting as an inability to read despite preservation of other aspects of language (such as spelling and writing).
Allocentric visual neglect	A form of neglect whereby the patient neglects their peri-personal or extrapersonal space. This is manifest as an inability to respond to, or recognize, stimuli presented on the contralateral side of the lesion, based on the midline of that object. Therefore, patients with allocentric neglect fail to respond to the contralateral side of individual objects.
Anomia	A form of aphasia manifesting as an inability to name everyday objects.
Apperceptive visual agnosia	A form of visual agnosia, involving an inability to name, match or discriminate objects presented visually.
Apraxia	A general term for a motor disorder manifesting as an inability to execure learned, purposeful movements (such as making a cup of tea).
Avoidance bias	A dependent measure used in obstacle avoidance which indicates whether the ipsilateral or contralateral obstacles had a greater influence on response transection point.
Avoidance sum	A dependent measure used in obstacle avoidance describing how much obstacle avoidance was observed.
Bálint's syndrome	A syndrome strongly associated with presentations of PCA, consisting of a triad of

	symptoms; simultanagnosia, optic ataxia and ocular apraxia.
Closed-loop	A term referring to pointing behavior with visual feedback (e.g. when the agent can see their hand during the pointing movement).
Closing-in behaviour	A term used to describe the tendency for a copy of an image to be drawn inappropriately close to, or on top of, the original image.
Constructional dyspraxia	A symptom describing impaired drawing or building performance, also referred to as visuo-constructional dyspraxia.
Contralateral obstacle position	A term to describe obstacles contralateral (opposite) to the dominant hand in the obstacle avoidance task.
Contralateral obstacle weighting	A dependent measure used in the obstacle avoidance task representing the relative weighting of the contralateral obstacle on the response endpoints.
Cost of local	A dependent measure used in the Navon task, providing a ratio of the RT cost of naming the local letter form with regard to naming the global letter form.
Cost of overlapping	A dependent measure used in the BORB Perception of Multiple Figures task, providing a ratio of the RT cost of naming the overlapping figures with regard to naming the non-overlapping figures.
Cost of pairs	A dependent measure used in the BORB Perception of Multiple Figures task, providing a ratio of the RT cost of naming paired figures with regard to naming the single figures.
Cost of Relief	A dependent measure used in the Navon task, providing a ratio of the RT cost of naming the relief letter form with regard to naming the global letter form.
Cueing effect	A dependent measure used in the Posner task, providing a measure of attention calculated from the RT cost of invalidly cued trials compared to validly cued trials.

Directional akinesia	A deficit in moving in a direction, usually contralateral to a hemispheric lesion.
Directional bisection error	A dependent measure used in bisection tasks, measuring the response error relative to the true midpoint of the stimulus.
Dressing apraxia	A specific form of apraxia manifesting as difficulties in dressing.
Dysarthria	A motor speech disorder resulting in poor articularion of phonemes.
Egocentric visual neglect	A form of neglect whereby the patient neglects their own body or personal space. This is manifest as an inability to respond to, or recognize, stimuli presented on the contralateral side of the lesion, based on the midline of their own body, head, or retina. Therefore, patients with egocentric neglect fail to respond to the contralateral side of space relative to their own body.
Endpoint weightings bias	A dependent measure used in the bisection task measuring the relative influence of the changing endpoints on the response position, with positive values indicating a greater influence of the right endpoint, and negative values indicating a greater influence of the left endpoint. A value of 0 indicates no bias.
Endpoint weightings sum	A dependent measure used in the bisection task measuring the total attention the participant is giving to the task, whereby a participant who is fully attending to the task and is therefore influenced equally by the changing positions of both the left and the right endpoints will demonstrate an EWS of 1.
Environmental agnosia	An inability to recognize familiar surroundings.
Finger agnosia	An inability to name the different fingers.
Gerstmann's syndrome	A syndrome consisting of the symptoms; agraphia, acalculia, left-right confusion and finger agnosia
Ideomotor apraxia	A disorder characterized by an inability to perform tool-use pantomimes (such as

	pretending to use cutlery), or meaningful gestures (such as waving).
Ipsilateral obstacle position	A term to describe obstacles ipsilateral (on the same side) to the dominant hand in the obstacle avoidance task.
Ipsilateral obstacle weighting	A dependent measure used in the obstacle avoidance task representing the relative weighting of the ipsilateral obstacle on the response endpoints.
Maximum aperture	A dependent measure used in grasping tasks measuring the maximum distance between the end of the thumb and forefinger during a matching movement.
Maximum grip aperture	A dependent measure used in grasping tasks measuring the maximum distance between the end of the thumb and forefinger during a grasping movement.
Neglect	A pathological inattention to one side of space (most commonly the left side, following right-sided lesions to the posterior parietal cortex). 'Neglect', unless otherwise specified within this thesis, refers to visual neglect.
Ocular apraxia	An inability to voluntarily guide eye movements, also referred to as oculomotor apraxia.
Open-loop	A term referring to pointing behavior with no visual feedback (e.g. when the agent cannot see their hand during the pointing movement).
Optic ataxia	A deficit in visually-guided reaching and grasping behaviour, manifesting as misreaching to peripheral targets, an inability to appropriately scale the hand when reaching for objects in the visual periphery, and a failure to account for peripheral obstacles when reaching.
Praxes	The plural of praxis, referring to the process by which cognition directs motor behaviour (planning and executing movements).
Simultanagnosia	A visuoattentional disorder manifesting as an inability to perceive multiple visual objects at once.

Contents

1. General Introduction

The World Health Organization (WHO) identified dementia as a major public health issue and a priority area for research in 2012 (World Health Organization, 2012). Dementia has been re-labelled by the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as 'major neurocognitive disorder', the identifying features of which are significant cognitive decline from a prior level of performance in one or more cognitive domains consequently leading to interference for individuals who otherwise have independence in everyday activities (American Psychiatric Association, 2013; Sachdev et al., 2014). Memory loss is the most characteristic symptom associated with dementia, along with language problems, disorientation, unstable mood, confusion, and behavioural changes (Alzheimer's Association, 2016; Winblad et al., 2016).

The term 'dementia' refers to a clinical syndrome, a pattern of symptoms which when commonly clustered are referred to as dementia. There are a number of different disease processes which can cause dementia, each of which has a distinct symptom profile and pattern of brain abnormalities. More than 47 million people worldwide have dementia, with 9.9 million new cases diagnosed each year (WHO, 2017). The WHO projections estimate that by 2030, the total number of people with dementia will be around 75 million, and by 2050 this figure will almost triple to 132 million people (WHO, 2017). Dementia is the leading cause of dependency and disability across the world (WHO, 2012; Korczyn & Vakhapova, 2007), and is considered to be "The Silent Epidemic" due to its increasingly high prevalence rates (Larson, Yaffe & Langa, 2013, p.2275; Beck, Benson, Scheibel, Spar & Rubenstein, 1982).

Alzheimer's disease (AD) is the most common cause of dementia, accounting for an estimated 50-80% of dementia cases (Alzheimer's Association, 2016; Winblad et al., 2016). The primary risk factor for AD is old age, therefore the prevalence of the disease is increasing due to ageing populations globally

(Winblad et al., 2016). Typical early behavioural symptoms of AD are memory problems, apathy, and depression (Alzheimer's Association, 2016; Raskin, Cummings, Hardy, Schuh & Dean, 2015; Lam, Masellis, Freedman, Stuss & Black, 2013). AD is associated with accumulations of specific proteins intra- and extracellularly (Irvine, El-Agnaf, Shankar & Walsh, 2008). Beta-amyloid peptide (Aβ) plaques are one such hallmark, and are found to form extracellularly and interfere with neuronal communication (Mohandas, Rajmohan & Raghunath, 2009; Alzheimer's Association, 2016; Jellinger & Attems, 2007). Another neuropathological hallmark of AD is the formation of an abnormal form of the protein tau (τ), which then accumulates within the neurons – forming neurofibrillary tangles (NFTs) – which block molecular transport within the cell, and therefore inhibit normal cell functions (Mohandas et al., 2009; Raskin et al., 2015; Liu, Liu, Iqbal, Grundke-Iqbal & Gong, 2008; Jellinger & Attems, 2007). The consequence of the formation of Aβ plaques and NFTs is ultimately cell death, therefore brain scans and autopsies of individuals with advanced AD demonstrate dramatic atrophy due to cell loss (Alzheimer's Association. 2016; Raskin et al., 2015; Jellinger & Attems, 2007).

AD is increasingly becoming a more common cause of death across the world. In the United States of America during 2010, 32% of all older adult deaths (65 years or older) were attributed to AD (Weuve, Herbert, Scherr & Evans, 2014). By 2050 the proportion of deaths in this age bracket due to AD pathology is projected to be 43% (Weuve et al., 2014). In the United Kingdom an eight-fold increase in recorded AD deaths was observed for males, with a twelve-fold increase seen in females, between 1985 and 2004 (Griffiths & Rooney, 2006). In fact, dementia is now the leading cause of death in England and Wales (Alzheimer's Society, 2017).

The second most common form of dementia is vascular dementia (VaD), accounting for around 10-20% of dementia cases. VaD refers to cognitive impairment which is attributed to cerebrovascular pathologies, such as stroke (Iadecola, 2013). Although VaD is relatively uncommon as the primary cause of

dementia, it is observed in around 50% of dementia cases as a 'mixed dementia', where there is evidence of both VaD (infarcts) and AD pathologies (Iadecola, 2013; Alzheimer's Association, 2016). Use of the term 'vascular dementia' is somewhat contentious, with some authors suggesting that 'vascular cognitive impairment' reflects more accurately the full range of cognitive changes which can arise from vascular pathologies (Iadecola, 2013; O'Brien & Thomas, 2015). Memory loss is not typically as prominent a symptom in VaD (although memory is affected to various extents within vascular dementia); more common presenting symptoms include impaired judgment or decision making, as well as difficulties with motor function, such as slowed gait and poor balance (O'Brien & Thomas, 2015; Alzheimer's Association, 2016).

Mixed dementia (MD), as the name suggests, is characterised by abnormalities associated with more than one cause of dementia, with VaD and AD being the most common form, followed by AD and Lewy Body dementia (LBD), then AD with vascular dementia and LBD, the rarest form is considered to be the co-occurrence of vascular dementia and LBD (Alzheimer's Association, 2016; Jellinger & Attems, 2007). There is some evidence suggesting that MD may be more common than previously estimated, with ranges from prospective and retrospective autopsy studies reporting between 2-58% prevalence of MD (Jellinger & Attems, 2007).

Dementia with Lewy bodies (DLB) typically presents with disturbances to sleep as well as vivid visual hallucinations, and shares the same pathophysiological basis as Parkinson's disease dementia (PDD), consequently patients will commonly demonstrate motor features of parkinsonism (Walker, Possin, Boeve & Aarsland, 2017; Walker, Possin, Boeve & Aarsland, 2015). DLB and PDD are considered to share a continuum of disease, and are therefore collectively referred to as LBD (Walker et al., 2017). Up to 80% of patients with Parkinson's disease will progress to dementia: those who show motor symptoms at least one year prior to the development of dementia will typically be diagnosed with PDD, whereas DLB is diagnosed when dementia precedes motor symptoms

(Walker et al., 2015; Stinton et al., 2015). LBD is characterised pathophysiologically by accumulations of the protein α-synuclein (Lewy bodies) within neurons although the process of cell death within LBD is not clear (Walker et al., 2015).

Clearly, dementia may be caused by numerous different disease processes, sometimes in combination, with various subtypes identified showing differences in age of onset, rate of decline, and profile of cognitive symptoms (Lam et al., 2013). Classifying the different mechanisms of disease presentation and progression will allow for targeted rehabilitation as well as the development of sensitive and specific screening tools to aid in quicker diagnosis. Interventions for dementia are most effective at the early stages of the disease, therefore rapid diagnosis can be beneficial, although pharmacological therapies provide relief for symptoms only, and do not prevent disease progression (Mueller et al., 2005; Chau, Liu, Ruthirakuhan, Lanctôt & Herrmann, 2017).

Posterior Cortical Atrophy (PCA) represents a particularly unusual variant of dementia, reported to account for 5% of AD cases, although the true incidence may be as high as 15% (Crutch et al., 2013, 2012; Lehmann et al., 2011). PCA is often caused by AD, although other pathological causes such as LBD, corticobasal degeneration (CBD) and Cruetzfeldt-Jacob disease have been recorded (McMonagle, Deering, Berliner & Kertesz, 2006; Mendez, Ghjarania & Perryman, 2002; Kirschner & Lavin, 2006; Meek, Shelton & Marotta, 2013; Beh et al., 2015). PCA is a rare, progressive dementia characteristically demonstrating a younger age of onset than typical AD, with patients often displaying fewer memory deficits, better verbal fluency, and greater insight into their diagnosis than those diagnosed with typical AD (Mendez et al., 2002). Further elaboration on the symptom profile of PCA is presented later in this thesis.

PCA was identified three decades ago by Benson and colleagues (PCA was formally known as 'Benson's syndrome') but relatively little dedicated research has been conducted on the disease in the years since (Benson, Davis & Snyder, 1988). There are still no formal diagnostic criteria available for PCA, although a recent paper by Crutch and colleagues represents the best systematic attempt to date at providing a classification framework (Crutch et al., 2017). In addition, there are no formal operational definitions of the visuomotor and visual attentional symptoms which are identified as characteristic of the disease, but these clearly include space and object perception deficits, simultanagnosia, and optic ataxia (Crutch et al., 2017). PCA is commonly misdiagnosed, most likely as the result of the combined effects of the relative rarity of the disease and the variable presentation, but also as a consequence of the patient often first seeking the opinion of an ophthalmologist whose tests do not usually identify cortical brain dysfunction (Crutch et al., 2013, 2012).

Evidence accumulated since the identification of PCA by Benson and colleagues has certainly made strides towards a better understanding of the disease, however the lack of distinct diagnostic criteria, clearly defined core symptoms with associated validated screening tools, in conjunction with the generally delayed pathway to diagnosis make the scientific study and clinical management of this disease even more challenging.

The primary aim of the series of experimental investigations presented within this thesis is to better characterise the visuomotor and visuoattentional abilities of patients with neurodegenerative diseases, with a particular focus on PCA. Each study is introduced within the relevant chapter by means of a thorough review of the relevant literature, with experimental aims provided.

2. Thesis Theory

2.0 Introduction

The primary aim of this thesis was to characterise the visuomotor and visuoattentional abilities of patients with posterior cortical atrophy, as well as those with related but different neurodegenerative diseases.

The investigations within this PhD project were divided into two phases. The first was a screening phase, the overarching aim of which was to serve as a novel assessment of patterns of cognitive symptoms in PCA as compared with other neurodegenerative diseases (NDDs), including Alzheimer's disease, Frontotemporal Dementia, Lewy Body Dementia, aphasia, and Corticobasal Degeneration, in order to improve future diagnostic targeting. The second phase comprised laboratory-based experimental investigations, aimed at providing a fine level of detail on the specific visuomotor and motor abilities of patients with PCA, as well as those with other NDDs. An additional clinical case study was conducted in order to serve as an 'NDD-free' comparator to performance on the laboratory-based assessments. Brain imaging results from the PCA patients tested within this thesis are also presented and discussed within the context of performance on the screening and lab-based assessments.

In addition to the clinical assessments, a systematic review of the literature was conducted as well as an additional study with healthy control participants in which optic ataxia was modelled using a visual attention and visuomotor dual task paradigm.

2.1 Screening Phase

The screening phase (Phase 1) was planned in order to get a general overview of the abilities and deficits of patients who took part in a range of visual and visual- attentional tasks. It was also intended to investigate which assessments were the most sensitive and specific to the deficits associated with PCA. The

primary aim of Phase 1 testing, therefore, was to establish the potential diagnostic utility of the assessments in discriminating patients with PCA from patients with other NDDs. The second aim was to investigate the frequency of primary visual and visual-attentional symptoms in patients with other NDDs.

2.2 Laboratory Phase

Patients who completed Phase 1 testing were invited to participate in two separate lab-based testing sessions (Phase 2A/2B) of approximately three hours duration each. These assessments took place at the Human Movement Laboratory within the University of Edinburgh's Department of Psychology. The assessments included were designed to provide a very fine level of detail on patients' visual, visuomotor and visual attentional abilities, achieved using a range of specialized recording equipment.

Age- and sex-matched healthy control volunteers were additionally recruited and tested on all Phase 2 assessments.

2.3 Systematic Review

The systematic review followed PRISMA reporting guidelines and methodology in order to ascertain which, if any, assessments of visual attention or visuomotor abilities are typically reported within literature specific to PCA.

This systematic review served a dual function. Firstly, it provided a general insight into how commonly (and how effectively) these symptoms have typically been assessed in patients with PCA – motivating the main aims of this PhD study as a whole. Secondly, the review provided some insight into what methodologies have been applied in the assessment of attention and visuomotor functions in patients with PCA previously.

2.4 Modelling Optic Ataxia

An additional study on healthy control participants was conducted in which the symptom of optic ataxia was modelled using a visual attentional task with concurrent reaching task. Attention and action have typically been characterised as separate processes, but this study supports an alternative theory, that visual attentional demand mediates visuomotor performance (Similä & McIntosh, 2014; Hesse & Deubel, 2011; Hesse, Schenk & Deubel, 2012).

The results of this study have clinical relevance as they suggest that visuomotor symptoms such as optic ataxia may be a consequence of visual attentional deficits. These results therefore present an interesting platform from which future studies could be built, perhaps by creating a more attentionally-demanding task at fixation to investigate whether this resulted in more magnified patterns of errors.

Creating a simple touchscreen test based on this, and future investigations, could form the basis for a diagnostic task capable of differentiating between different diagnoses, potentially sensitive to very small, early-onset deficits in visual attention, which may otherwise go undetected.

3. Systematic Review

3.0 Background

3.0.1 Introduction

Posterior Cortical Atrophy (PCA) is a rare, progressive dementia characterised by various visuospatial and visuoperceptual impairments in tandem with often intact visual acuity (Aresi & Giovagnoli, 2009; Meek, Shelton & Marotta, 2013; Crutch et al., 2012; Crutch et al., 2017). Neurological symptoms commonly associated with PCA include alexia, apperceptive visual agnosia, Bálint's syndrome (simultanagnosia, optic ataxia and ocular apraxia), Gerstmann's syndrome (agraphia, acalculia, left-right confusion as well as finger agnosia), ideomotor apraxia, anomia, visual field deficits, and environmental agnosia (Meek, Shelton & Marotta, 2013; Crutch et al., 2012; Crutch et al., 2017). For patients, these symptoms manifest in daily life as problems with writing, reading, drawing, identification of letters and numbers, recognising and using objects, and getting lost in familiar environments (Aresi & Giovagnoli, 2009). Visual hallucinations are additionally reported in approximately 25% of PCA patients (Caixeta et al., 2013) and spontaneous Parkinsonian symptoms are also occasionally noted (Meek et al., 2013). These less common symptoms are often reported later in the course of the disease and may be indicative of the underlying pathology, such as Lewy Body Dementia (Meek et al., 2013).

Patients with PCA typically display fewer memory deficits, better verbal fluency, and greater insight into their diagnosis than those diagnosed with typical AD (Mendez et al., 2002). The progressive deterioration of a relatively isolated domain of cognition is rarely seen in typical AD, whereas PCA is characterised by predominant initial symptoms demonstrating impairment of higher order visual functions, out of proportion to impairment of other cognitive domains (Andrade et al., 2010; Meek et al., 2013; Nestor, Cine, Fryer, Clarke & Hodges, 2003; Ardila, Rosselli, Arvizu & Kuljis, 1997). In AD, visual disturbances

typically occur much later in the course of the disease after considerable progression, at which point other cognitive abilities such as memory are severely affected, whereas visual disturbances are an early clinical feature of PCA (Aresi & Giovagnoli, 2009).

In PCA neurodegeneration typically has its genesis in the primary visual cortex extending through the dorsal visual association cortex (Andrade et al., 2010; Meek et al., 2013; Nestor, Cine, Fryer, Clarke & Hodges, 2003). As the disease progresses to anterior regions of the brain, cognitive losses become increasingly prominent (Meek et al., 2013). Indeed, clinical presentations of PCA and typical AD may converge at later stages (Lehmann et al., 2012). For this reason, and based on post-mortem examinations, PCA is often characterised as a clinical syndrome for which AD is often – but not exclusively – the pathological cause (Caixeta, Taleb, Ghini, Dias Soares, de Melo Caizera & Vargas, 2013). Other pathological causes identified in PCA include Creutzfeldt-Jacob Disease, corticobasal degeneration, and Lewy Body Dementia (McMonagle, Deering, Berliner & Kertesz, 2006; Mendez, Ghjarania & Perryman, 2002; Kirschner & Lavin, 2006; Mendez, Ghajarania & Perryman, 2002; Meek, Shelton & Marotta, 2013; Beh et al., 2015).

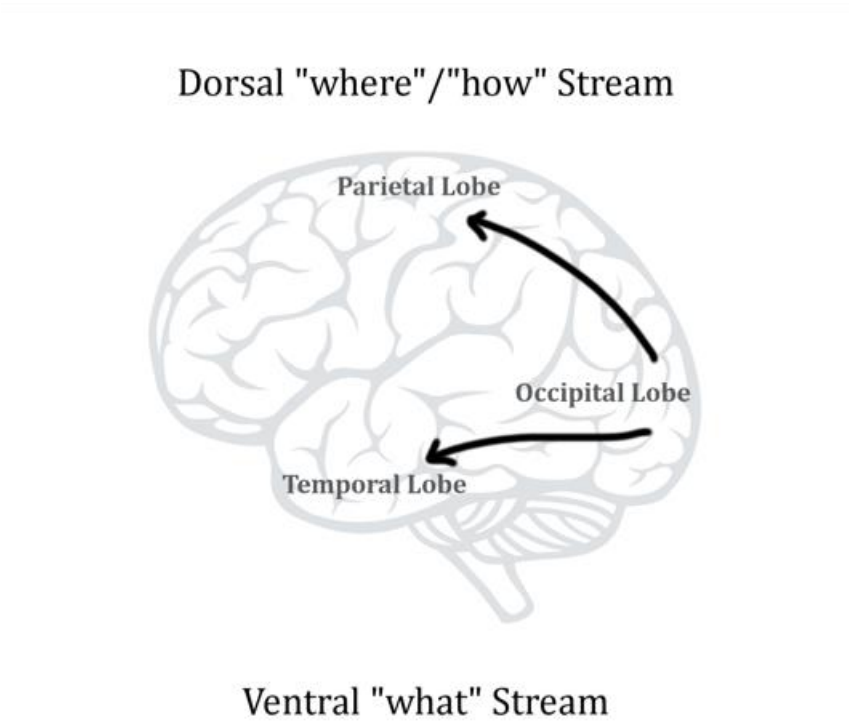


Figure 3.1: Simplified Diagram of Dual Streams of Visual Processing, as proposed by Goodale & Milner (1992) and Milner & Goodale (2008).

Case studies of PCA typically describe symptoms consistent with damage to the dorsal stream of visual processing, according to the dual stream hypothesis of visual processing (Goodale & Milner, 1992; Milner & Goodale, 1995; Milner & Goodale, 2008). This theory proposes that the occipito-parietal dorsal pathway processes egocentric spatial ("where") information, while the occipito-temporal ventral stream processes more object identification ("what") information (Figure 3.1) (Goodale & Milner, 1992; Milner & Goodale, 2008). The dorsal stream has close ties to the motor system and codes the location and movement features of objects in order to allow the agent to acquire or act upon the object, which has led to this dorsal stream also being characterised as a "how" pathway (Possin, 2010; Goodale & Milner, 1992). The posterior parietal cortex in each hemisphere is organised mainly for contralateral spatial functions, although there is a dominant role for the right hemisphere in dorsal stream spatial functions (Possin, 2010). Dorsal stream symptoms observed in PCA patients include prominent spatial processing disturbances and features of Bálint's syndrome, like optic ataxia (Nestor, Caine, Fryer, Clarke & Hodges, 2003). There

are also occasional case studies which report symptoms consistent with a 'ventral variant' of PCA, including presentations of visual object agnosia and prosopagnosia (Nestor et al., 2003; McMonagle, Deering, Berliner & Kertesz, 2006). The ventral stream pathway projects from the ventral occipital cortex into the inferior temporal cortex and codes spatial characteristics of objects relevant to their identity such as colour and form (Possin, 2010). A limited number of studies have investigated evidence for dorsal/ventral discrete subtypes of PCA, and there is some evidence to suggest that two mostly non-overlapping syndromes of these types can occur within PCA (although it is unclear whether these differences represent distinct disease subtypes or simply points on a functional continuum of variation within PCA), however the ventral functional presentation is reported as appearing to be more rare (Tsai, Teng, Lui & Mendez, 2011; Caine, 2010; Spehl et al., 2015; Ross et al., 1996).

Despite being identified almost 30 years ago by Benson, Davis & Snyder (1988), research into PCA is still in its infancy when compared to the understanding of typical AD. The characteristically young age of onset, as well as the rarity and variable clinical features of PCA – particularly in light of what is often reported as normal visual acuity, as well as the common comorbidity of a mood disorder – all contribute to the concerning rates of misdiagnosis of this disease (Beh et al., 2015). Such features, it has been suggested, may lead even experienced neurologists to misdiagnose true PCA patients as 'anxious' or 'functional' (Beh et al., 2015).

A recently published paper by Crutch and colleagues proposes a classification framework for PCA as a step towards developing formal definitions of the diagnostic, clinical, and neuroimaging features of the disease (Crutch et al., 2017). Further discussion and elaboration on this framework are presented in Chapter 4. However, relevant to the present review and notable within the classification framework is the prominence of attentional and visuomotor symptoms within the core symptoms identified by Crutch and colleagues (Crutch et al, 2017). Indeed, within the top ten most common symptoms are

four visual attentional symptoms ('space perception deficit', simultanagnosia, object perception deficit, and environmental agnosia) and three visuomotor symptoms (constructional dyspraxia, dressing apraxia, and optic ataxia). Clearly, visual attentional and visuomotor deficits could be considered cardinal to the profile of PCA (Crutch et al., 2017).

The present systematic review aims to investigate the use of visual attention or visuomotor-specific assessments in the evaluation of patients with PCA, as deficits within these domains are the most frequently associated with PCA (Crutch et al., 2017). Specifically, this review will seek to investigate evidence of the assessment of dorsal-stream mediated visual attentional and visuomotor symptoms, such as optic ataxia, neglect, and simultanagnosia. This will demonstrate the level of detail on the characteristics of these specific symptoms that is currently available to PCA researchers, and will then provide a better context for the broader investigations of this thesis.

3.0.2 Research Question

To what extent do papers investigating and reporting on Posterior Cortical Atrophy (PCA) report the use of assessments specific to visual attention or visuomotor symptoms.

3.0.3 Aims

The aim of this systematic review is to summarize all the literature addressing visual attention or visuomotor specific symptoms within PCA. The broader aim of this review is to investigate with what frequency investigations into PCA are addressing these highly indicative symptoms, and what assessments are being used to do so.

3.1 Method

This systematic review was completed in accordance with published PRISMA guidelines (Moher, Liberati, Tetzlaff, Altman & PRISMA Group, 2009). The completed checklist is presented in Appendix 1.

3.1.1 Eligibility Criteria

The candidate literature on PCA is relatively small, so relevant articles were selected by hand, using the inclusion and exclusion criteria listed in Table 3.1 below.

Inclusion Criteria	Exclusion Criteria
• Reporting of assessment, or description of, visual attention symptoms in PCA, specifically: optic ataxia, neglect, closing-in behaviour and/or simultanagnosia.	• Article is a conference proceeding/correction/commentary on a previous article
• Reporting of assessment, or description of, visuomotor symptoms in PCA. Specifically, deficits in visually-guided reaching, grasping, and/or automatic avoidance of obstacles (deficits of which may indicate optic ataxia), and closing-in behavior or magnetic misreaching (which may be indicative of deficits in visual attention).	• Article is a review
• Paper may address PCA concurrently with other AD or dementia subgroups as long as attention or visuomotor symptoms (as detailed above) are specifically investigated	• Article addresses only Alzheimer's disease or dementia, not specific to PCA
	• Article not available in English

Table 3.1: Inclusion and Exclusion Criteria for Systematic Review

Table 3.5 in Section 3.2.2 presents the assessments identified as being specific to visual attention or visuomotor abilities, reported within the systematically reviewed papers.

3.1.2 Information Sources

The main search was conducted on the 12th February, 2015. The electronic databases used were MEDLINE (including Ovid MEDLINE in process + other non-indexed citations + MEDLINE, EMBASE and PSYCHINFO) and SCOPUS.

3.1.3 Search Strategy

A scoping exercise was conducted on the 12th February, 2015 to investigate the extent of the literature and to identify the most relevant keywords to use for the formal search.

No medical subject headings were available on the PubMed MeSH database for any of the following relevant terms; "posterior cortical atrophy", posterior cortical atrophy, visuomotor, "motor symptoms", or motor symptoms.

Therefore the following keyword phrase was used in the database search "posterior cortical atroph*".

Note that the descriptors of "motor symptoms", or motor symptoms, were included in order to ensure that any additional papers addressing motor symptoms which relate to visuomotor control were not omitted.

3.1.4 Study Selection

Following the use of the search criteria outlined in Sections 2.1.1 – 2.1.3, duplicate articles were removed. A total of 1010 articles were identified by the database searches: 603 of these articles were duplicates and subsequently removed, leaving 407 which were taken to the next stage of study selection

Study selection then proceeded in two separate stages. In the first stage, the title and abstract of each article were independently screened by two reviewers, Harriet Ingle (HI) and Ratko Radakovic (RR). The reviewers classified the

articles as ‘to be excluded’, ‘to be included’ or ‘ambiguous’. The reviewers then met to discuss the results of their independent screens. Any disagreements between classifications as well as any articles identified as ‘ambiguous’ were resolved through discussion between the reviewers and by close scrutiny of the article against the stated inclusion and exclusion criteria for the review. A total of 407 articles were screened as part of this initial stage, which led to the exclusion of a further 385 articles which did not meet the inclusion criteria. Therefore, 22 articles were progressed to the second stage of screening.

In the second stage, the 22 articles which had been identified for inclusion from the first stage, were then read in their entirety by both HI and RR independently. As with the first stage of review, the reviewers classified the articles as ‘to be excluded’, ‘to be included’ or ‘ambiguous’. Again, following a meeting between the two reviewers, the results of this second stage of screening were discussed and the final articles to be included in the review were agreed. This second stage of screening led to the exclusion of a further 12 articles, therefore 10 articles were included for systematic review.

For both the first and the second stage of reviewing, a unanimous agreement was required to be reached on the classification of each article.

3.1.5 Data Collection

Data were collected using a data extraction form created by HI, which was based on adapted information from Wright, Brand, Dunn & Spindler (2007). The data extraction form is presented in Appendix 2.

3.1.6 Methodological Quality Appraisal

The 10 articles selected for systematic review were subjected to an observational study quality assessment tool (OSQAT), adapted from a tool developed by Weightman, Mann, Sander & Turley (2004, p.26).

Criteria	Yes	No	Other*
1. Is the study relevant to the needs of the Project?			
2. Does the paper address a clearly focused issue? in terms of: · the population studied? · (case-control study only) is the case definition explicit and confirmed? · the outcomes considered? · are the aims of the investigation clearly stated?			
3. Is the choice of study method appropriate?			
4. Is the population studied appropriate? · (cohort study) Was an appropriate control group used – i.e. were groups comparable on important confounding factors? · (case-control study) Were the controls randomly selected from the same population as the cases?			
5. (Cohort study) Was follow up for long enough? · Could all likely effects have appeared in the time scale? · Could the effect be transitory? · Was follow up sufficiently complete? · Was dose response demonstrated? · (retrospective/longitudinal case study) Was the case study conducted over a long enough time period to get a detailed overview of symptom progression?			
6. Are tables/graphs adequately labelled and understandable?			
7. Are you confident with the authors' choice and use of statistical methods, if employed?			
8. What are the results of this piece of research? Are the authors' conclusions adequately supported by the information cited?			

Table 3.2: OSQAT Tool for Quality Appraisal of Studies
* Other: NA = Not Applicable, CD = Could not determine.

No standardized scoring system was suggested by Weightman et al. (2004) for the quality assessment tool used in the present review, therefore studies were categorized according to the number of items which were answered with 'yes'. Table 3.3, below, presents the rating classifications.

No. of 'yes' items	Classification
6-8	Very good
4-6	Good
2-4	Poor
0-2	Very poor

Table 3.3: OSQAT Score Classifications

3.2 Analysis

3.2.1 Summary Measures

The main summary measures for this systematic review were clustered under two themes. Each measure extracted using the data extraction form is presented below.

- Study Overview/Methods:
    - Author (year)
    - Time Scale
    - Research design
    - Comparison or control group
    - Patient group characteristics
    - PCA Diagnostic criteria
    - Inclusion/Exclusion Criteria
    - Specific PCA symptoms under investigation

- Results:
    - Were validated outcome measures used?
    - Were tests of visual attention used?
    - Tests of visual attention
    - Were tests of visuomotor abilities used?
    - Tests of visuomotor abilities

These measures are summarized in clusters for simplicity of presentation in Sections 2.3.3 – 2.3.6. Details of which measures were reported under each cluster heading are presented below in Table 3.4.

Cluster Heading	Measures Reported
Study Design & Demographic Information	• Time Scale • Research design • Comparison or control group • Patient group characteristics
Diagnostic, Inclusion and Exclusion Criteria and PCA-Specific Symptoms Investigated	• PCA Diagnostic criteria • Inclusion/Exclusion Criteria • Specific PCA symptoms under investigation
Outcome Measures, Tests of Visual Attention and Tests of Visuomotor Abilities	• Were validated outcome measures used? • Were tests of visual attention used? • Tests of visual attention • Were tests of visuomotor abilities used? • Tests of visuomotor abilities

Table 3.4: Extracted Measures: Cluster Headings Reporting Guide

3.2.2 Assessments of Attention and Visuomotor Abilities

Table 3.5, below, presents the assessments which were identified as specific to visual attention or visuomotor abilities from the extracted papers.

Assessment Category	Target Symptom	Test Name	Frequency
Attention			
	Neglect	Line Cancellation Test	2
		Line Bisection Test	2
		Mesulam Letter Cancellation Test	1
		Schekenberg Line Bisection Test	1
		Clock Drawing	1
		Boston Cookie Theft Picture	2
	Neglect/Simultanagnosia	Visuoperceptual Analysis/Synthesis – Overlapped figures test	1
		Rey-Osterriech Complex Figure	1
	Simultanagnosia/Figure-ground discrimination deficits	Southern California Figure-ground Test	1
	Figure-ground discrimination deficits	Hooper Visual Organisation Test	2
	Visual agnosia	Visual form discrimination Test	1
		Weigl's Sorting Test	1
		Perception of Degraded Figures (15 incomplete Gollin Figures)	1
	Visual attention deficits NOS	TMT – A	2
		WAIS-R – Picture Completion Subtest	1
		WAIS-R – Block Design Subtest	1
		Attentive Matrices	1
Visuomotor			
	Optic ataxia	Grasping Efron Blocks in different visual conditions	1
		Optic ataxia assessment (point to and trace pictures)	1
		"manual tasks under visual guidance bilaterally" (assumed to be test of optic ataxia)	1
	Apraxia	Apraxia/dressing apraxia	1
	Directional akinesia	Test for directional akinesia (described by Heilman et al., 1983).	1
	NOS	'Visuospatial' task reported but not defined (may be visuomotor)	1

Table 3.5: Assessments of Visual Attention and Visuomotor Abilities Reported in Reviewed Papers

Note: Many of these tests could be assigned multiple categories, therefore for simplicity tests have been organised into categories which they are most commonly associated with.
Key: NOS = not otherwise specified.

3.2.3 Synthesis of Results

In order to summarize these data, results are reported both in the form of tables and narratively within the results section. Research specific to PCA is still uncommon, and consistency of method and of result reporting across studies is low. Therefore it was not possible to conduct a meta-analysis of the papers under review.

Instead, this review presents a narrative synthesis of the papers examined. Articles were summarized in groups under two main categories; papers which presented a diagnostic-descriptive account, and those which were experimental in nature. Experimental papers were defined as those which tested explicitly stated research hypotheses with at least two groups. Within the diagnostic-descriptive category, a further distinction between case studies (single or multiple) and group studies was made. Results are presented separately for each of the three research categories.

One paper in particular crossed the boundaries somewhat between diagnostic-descriptive and experimental classifications. It was decided that this paper should be classified as an experimental study, as the case study was supplementary to the experiment described (Cohen, Burtis, Cheol Kwan, Williamson & Heilman, 2010).

An additional section, Section 3.7, is presented, which provides updated details on research literature which meet the inclusion criteria for review, but which were published after the initial database search.

3.2.4 Additional Analysis

Two additional streams of analysis, which did not form part of the main systematic review, are reported as they were considered a helpful contribution to the literature on PCA.

The first of these additional analyses is a qualitative overview of the frequency of validated neuropsychological assessments reported in papers specific to PCA. This was conducted on any PCA-specific paper identified from the database search in which the use of neuropsychological assessments were reported (n = 40). This was intended to provide a general overview of which standardised neuropsychological assessments are reported within the existing literature on PCA.

In order to provide as much insight into PCA as possible – particularly in light of the fact that it is still a very under-researched area – a second additional stream of analysis is presented which provides data on the presenting symptoms (first wave) reported across all articles systematically reviewed (n = 10), as well as symptoms reported at a second assessment (second wave), where reported. These data are presented in Section 3.7.2.

3.3 Results of Study Selection Process

3.3.1 Study Selection

Figure 3.2 below presents a flow diagram of article selection. Table 3.6 presents an overview of the categories of the 274 PCA-specific articles which did not meet the inclusion criteria for review.

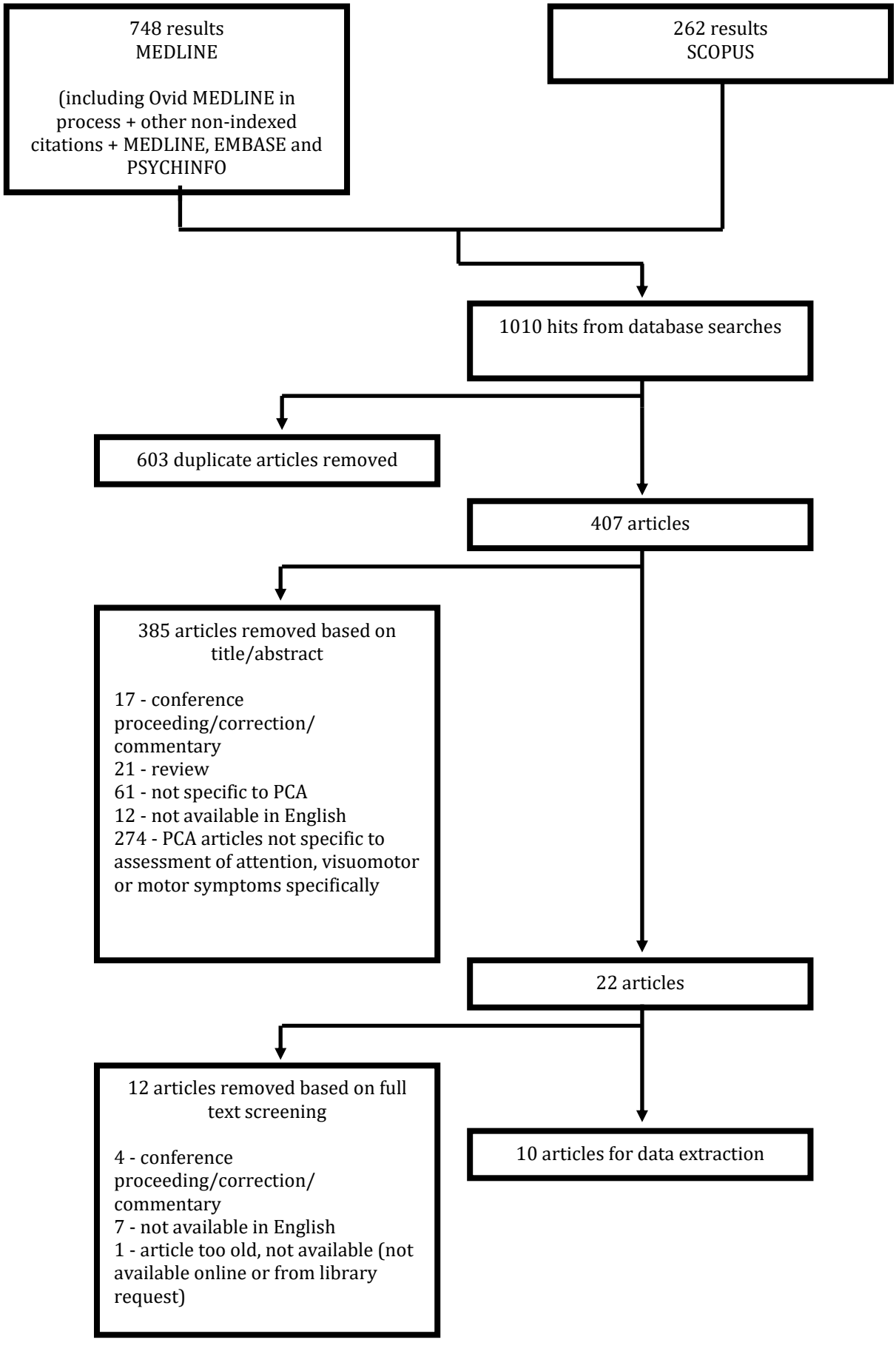


Figure 3.2: Systematic Review Article Selection Flow Diagram

PCA Articles Removed at Review Stage 1: Theme/Focus	Frequency
Histology/imaging/structural	151
Other symptoms in PCA (mood/language/memory)	101
Drug (or other) therapy/assessment	12
Genetic	10
Total	274

Table 3.6: Theme/Focus of PCA Articles Removed During First Stage of Review

The 274 PCA-specific articles which did not meet criteria to be included in the main review were screened qualitatively in order to provide insight into which neuropsychological assessments are commonly used in the assessment of PCA patients. Results of this screen are presented in Section 3.7.1.

3.3.2 Quality Appraisal

Table 3.7 presents the results of the OSQAT appraisal of the reviewed studies.

Author(s) (Year)	1	2	3	4	5	6	7	8	Overall Quality
Ardila, Rosselli, Arvizu, & Kuljis, 1997	Y	Y	Y	NA	NA	Y	NA	Y	Good
Aresi & Giovagnoli (2009)	Y	Y	Y	CD	Y	Y	Y	Y	Very good
Benson, Davis, & Snyder, 1988	Y	Y	Y	NA	Y	Y	NA	Y	Very good
Caixeta, Taleb, Ghini, Dias Soares, de Melo Caixeta, & Vargas, 2013	Y	Y	Y	NA	NA	Y	N	N	Good
Cohen, Burtis, Cheol Kwan, Williamson & Heilman, 2010	Y	Y	Y	NA	Y	Y	N	Y	Very good
Hsu, Chen, & Chiu, 2004	Y	Y	Y	NA	Y	Y	N	Y	Very good
Meek, Shelton & Marotta, 2013	Y	Y	Y	NA	Y	Y	Y	Y	Very good
Mendez, Ghajarania & Perryman, 2002	Y	Y	Y	Y	Y	Y	Y	Y	Very good
Nagratnam, Nagratnam, Jolley, & Ting, 2001	Y	N	Y	NA	NA	Y	NA	Y	Poor
Rogelet, Delafosse & Destee, 1996	Y	Y	Y	NA	Y	NA	NA	Y	Good

Table 3.7: OSQAT Methodological Quality Appraisal of Review Studies
Note: NA = not applicable, CD = could not determine.

3.4 Synthesis of Results: Diagnostic-descriptive Studies (Single or Multiple Case Studies)

3.4.1 Study Design & Demographic Information

Author(s) (Year)	Time Scale	Single or Multiple Case Study	Comparison or Control Group	Patient Group Characteristics	Patient Demographic Summary
Ardila et al. (1997)	Cross-sectional	Single	N	1 PCA	F, age 65 years
Benson et al. (1988)	Longitudinal	Multiple	N	5 PCA	3F, 2M, mean age 61.8 ± 8.23 years
Caixeta et al. (2013)	Cross-sectional	Single	N	1 PCA	F, age 55 years
Hsu et al. (2004)	Longitudinal	Single	N	1 PCA	F, age 57 years
Nagratnam et al. (2001)	Retrospective	Multiple	N	5 PCA	1F, 4M, mean age 68.6 ± 8.59 years
Rogelet et al. (1996)	Retrospective	Multiple	N	2 PCA	1F, 1M, age 61 and 51 years

Table 3.8: Study Design & Demographic Overview of Diagnostic-Descriptive Studies (Single or Multiple Case Studies)

Cross-sectional, longitudinal, and retrospective research designs were equally represented across diagnostic-descriptive studies (n = 2 for each). The range of PCA patients reported was between one and five. Therefore, most case studies under review were concerned with small numbers of PCA patients. Across all case studies females and males were approximately equally represented, with eight females and seven males reported. The mean age of patients across all case studies was 62.73 years (SD = 8.37). Table 3.8, above, summarizes these data.

3.4.2 Diagnostic, Inclusion and Exclusion Criteria and PCA-Specific Symptoms Investigated

Author(s) (Year)	D. Criteria Defined	Basis of D. Criteria		Inclusion / Exclusion Criteria Defined	Basis of Inclusion / Exclusion Criteria		Target Symptoms Defined	Target Symptoms
		I	C		I	C		
Ardila et al. (1997)	Y	•		Y			Y	Reading, writing, attention, language, memory, reasoning abilities
Benson et al. (1988)			•	N		•	N	
Caixeta et al. (2013)	N			Y			Y	Opthamologic symptoms
Hsu et al. (2004)	N			N			N	
Nagratnam et al. (2001)	Y	•	•	Y	•		Y	Bálint's syndrome
Rogelet et al. (1996)	N			Y			Y	Visuospatial & visuo-perceptual symptoms

Table 3.9: Diagnostic, Inclusion and Exclusion Criteria and PCA-Specific Symptoms Investigated of Diagnostic-Descriptive Studies (Single or Multiple Case Studies)
Key: D. = Diagnostic, Y = Yes, N = No, I = Imaging, C = clinical/behavioural history or presentation, • = presence of diagnostic criteria

Three studies did not define the diagnostic criteria used to identify PCA patients (Rogelet, Delafosse & Destee, 1996; Hsu, Chen, & Chiu, 2004; Caixeta, Taleb, Ghini, Dias Soares, de Melo Caixeta, & Vargas, 2013). One study used imaging results diagnostically in order to define PCA, whereby atrophy to the occipito-patietal and occipito-temporal regions with relative sparing to the calcarine and pericalcarine regions was considered indicative of PCA (Ardila, Rosselli, Arvizu, & Kuljis, 1997). One study used DSM-III criteria for primary degenerative dementia with supplementary imaging data in order to define PCA (Nagratnam, Nagratnam, Jolley, & Ting, 2001). The final case study paper identified patients on the basis of their clinical history and behavioural presentation, although it should be noted that it was this paper which first defined PCA as a clinical

syndrome – therefore, strictly speaking, this paper did not use diagnostic criteria but rather helped to establish them (Benson, Davis, & Snyder, 1988).

Four of the six diagnostic-descriptive case study papers did not state inclusion or exclusion criteria (Ardila, Rosselli, Arvizu, & Kuljis, 1997; Caixeta, Taleb, Ghini, Dias Soares, de Melo Caixeta, & Vargas, 2013; Hsu, Chen, & Chiu, 2004; Rogelet, Delafosse & Destee, 1996). The seminal paper by Benson and colleagues defined the inclusion criteria based on a clinical and behavioural history, and Nagratnam and colleagues defined inclusion criteria based on imaging results, whereby patients were included upon satisfaction of CT scan incidence of PCA (not further defined), without impairment of ocular fixation (Benson, Davis, & Snyder, 1988; Nagratnam, Nagratnam, Jolley, & Ting, 2001).

Two case study articles did not define specific target symptoms, but rather presented a detailed description of patients with reference to many symptom types (Hsu, Chen, & Chiu, 2004; Benson, Davis, & Snyder, 1988). The other four articles investigated a range of symptoms relating to PCA, including; reading and writing disturbances, attention, language, memory and reasoning abilities (Ardila, Rosselli, Arvizu, & Kuljis, 1997) Bálint's syndrome (Nagratnam, Nagratnam, Jolley, & Ting, 2001), opthamologic symptoms (Caixeta, Taleb, Ghini, Dias Soares, de Melo Caixeta, & Vargas, 2013), and visuospatial and visuoperceptual symptoms (Rogelet, Delafosse & Destee, 1996).

3.4.3 Outcome Measures, Tests of Visual Attention and Tests of Visuomotor Abilities

Author(s) (Year)	Validated outcome measure(s) used	Test of visual attention used	Test of visuomotor abilities used
Ardila et al. (1997)	Y	Y	N
Benson et al. (1988)	N	N	N
Caixeta et al. (2013)	Y	Y	Y
Hsu et al. (2004)	Y	N	N
Nagratnam et al. (2001)	Y	N	Y
Rogelet et al. (1996)	N	N	Y*

Table 3.10: Outcome Measures, Tests of Visual Attention and Tests of Visuomotor Abilities: Diagnostic-Descriptive Studies (Single or Multiple Case Studies)
*Note that the task described in this study was described as visuospatial, therefore may or may not be visuomotor.

Validated outcome measures were used in four of the six case study articles (Ardila, Rosselli, Arvizu, & Kuljis, 1997; Caixeta, Taleb, Ghini, Dias Soares, de Melo Caixeta, & Vargas, 2013; Hsu, Chen, & Chiu, 2004; Nagratnam, Nagratnam, Jolley, & Ting, 2001). The remaining two papers did not report any validated outcome measures, but instead described clinical neurological-style examinations (Benson, Davis, & Snyder, 1988; Rogelet, Delafosse & Destee, 1996).

Only two studies applied tests of visual attention (Ardila, Rosselli, Arvizu, & Kuljis, 1997; Caixeta, Taleb, Ghini, Dias Soares, de Melo Caixeta, & Vargas, 2013). Ardila and colleagues reported using subtests of the WAIS-R, TMT, Visual Form Discrimination Test, Hooper Visual Organisation test and Rey-Osterrieth Complex Figure as well as a reported 'visuoperceptual analysis/synthesis' test consisting of an overlapping figures test, a cancellation and line bisection task, and a clock drawing task (Ardila et al., 1997). Caixeta and colleagues reported using the Hooper Visual Organisation Test, the Biscuits Theft Figure (sic) - assumed to be the Boston Cookie Theft Picture, and the TMT-A.

Three case studies reported tests of visuomotor abilities. Descriptions of the visuomotor tasks included in each study were limited, for example one study described only using a 'visuospatial test', which may or may not have been

visuomotor (Rogelet, Delafosse & Destee, 1996). Caixeta and colleagues provided a similarly limited report of 'manual tasks under visual guidance bilaterally' as a description of a visuomotor task used to assess optic ataxia (Caixeta, Taleb, Ghini, Dias Soares, de Melo Caixeta, & Vargas, 2013). The final visuomotor task reported within the case study group of articles was a task where patients were instructed to point to a picture and subsequently trace a picture in order to assess for symptoms of optic ataxia (note that no details on how performance on these tasks were scored were provided by the authors) (Nagratnam, Nagratnam, Jolley, & Ting, 2001).

3.5 Synthesis of Results: Diagnostic-descriptive Studies (Group Comparison Studies)

3.5.1 Study Design & Demographic Information

Author(s) (Year)	Time Scale	Comparison or Control Group	Patient Group Characteristics	Patient Demographic Summary
Aresi & Giovagnoli (2009)	Cross-sectional	Y	17 PCA, 17 non-PCA dementia (probable AD)	PCA: 11F, 2M, mean age 59.12 ± 6.09 years
Mendez et al. (2002)	Retrospective	Y	15 PCA, 30 probable AD (1 PCA double matched to 2 AD patients based on age, gender, and duration of illness)	PCA: 6F, 9M mean age 62.7 ± 6.4 years pAD: 12F, 18M, age within ± 5 years, and ± 2 years for duration of dementia

Table 3.11: Study Design & Demographic Overview of Diagnostic-Descriptive Studies (Group Comparison Studies)

One study used a cross-sectional research design, while the other employed a retrospective approach. Both of the articles used clinical control groups; these were the only articles within the pool of 10 papers which did so. Mendez, Ghajarania & Perryman (2002) tested 15 patients with PCA and recruited 30 probable AD patients as a control group, double-matched based on age, gender and duration of illness. Aresi & Giovagnoli (2009) tested 17 patients with PCA, and 17 non-PCA dementia patients (noted as probable AD). There was a slightly

greater frequency of female patients with PCA (n = 17) than males (n = 11) across group comparison studies. Patient ages were not reported individually therefore a mean age across group comparison studies could not be calculated, however, reported mean ages for each group study were 59.12 years (SD = 6.09) and 62.7 years (SD = 6.4) (Aresi & Giovagnoli, 2009; Mendez, Ghajarania & Perryman, 2002).

3.5.2 Diagnostic, Inclusion and Exclusion Criteria and PCA-Specific Symptoms Investigated

Author(s) (Year)	D. Criteria Defined	Basis of D. Criteria		Inclusion / Exclusion Criteria Defined	Basis of Inclusion / Exclusion Criteria		Target Symptoms Defined	Target Symptoms
		I	C		I	C		
Aresi & Giovagnoli (2009)	Y	•	•	N			Y	Visuospatial abilities, abstract reasoning, memory, language, executive functions, praxes.
Mendez et al. (2002)	Y	•	•	Y		•	N	

Table 3.12: Diagnostic, Inclusion and Exclusion Criteria and PCA-Specific Symptoms Investigated of Diagnostic-Descriptive Studies (Group Comparison Studies)
Key: D. = Diagnostic, Y = Yes, N = No, I = Imaging, H = histological, C = clinical/behavioural history or presentation, • = presence of diagnostic criteria

Both group comparison studies under review used a combined approach of clinical behavioural indicators of PCA (presenting symptoms such as a visual complaint without impairment in visual acuity) as well as imaging results using combinations of MRI, CT, PET and SPECT scan data revealing abnormalities in the occipito-parietal and occipito-temporal regions (Aresi & Giovagnoli, 2009; Mendez, Ghajarania & Perryman, 2002).

One paper failed to define inclusion or exclusion criteria beyond the diagnostic information used for PCA (Aresi & Giovagnoli, 2009). The second group

comparison study paper, however, defined broad inclusion criteria of patients presenting to outpatient neurology clinics – presumably, although not explicitly stated, within the Los Angeles area – with progressive visual complaints (without primary visual disturbances) between 1994-2001 (Mendez, Ghajarania & Perryman, 2002).

One article did not specify which PCA symptoms were under investigation specifically, but rather presented a comparison between PCA and typical AD on a range of measures, including neurobehavioural, epidemiological, and magnetic resonance imaging measures (Mendez, Ghajarania & Perryman, 2002). The second group-comparison study investigated specific visuospatial abilities and attention (typically impaired in PCA) as well as measures of abstract reasoning, memory, language, executive functions and praxes (Mendez, Ghajarania & Perryman, 2002).

3.5.3 Outcome Measures, Tests of Visual Attention and Tests of Visuomotor Abilities

Author(s) (Year)	Validated outcome measure(s) used	Test of visual attention used	Test of visuomotor abilities used
Aresi & Giovagnoli (2009)	Y	Y	N
Mendez et al. (2002)	Y	Y	Y

Table 3.13: Outcome Measures, Tests of Visual Attention and Tests of Visuomotor Abilities: Diagnostic-Descriptive Studies (Group Comparison Studies)

Both group comparison articles used validated outcome measures and at least one test of visual attention in the assessment of patients with PCA. Aresi & Giovagnoli reported the use of Weigl's Sorting Test and Attentive Matrices (2009). Mendez and colleagues reported the use of target cancellation (Mesulam Letter Cancellation Test) and line bisection (Schekenberg Line Bisection Test), as well as perception of degraded figures (15 incomplete Gollin figures), figure-ground discrimination (16 item Southern California Figure-Ground Test) and the Boston Cookie Theft Picture (Mendez, Ghajarania & Perryman, 2002).

Only one article reported tests of visuomotor abilities, specifically assessments of apraxia (responses to verbal commands including 16 transitive and intransitive actions of both upper limbs) and dressing apraxia (ability to put on an item of clothing with the sleeve inside out) (Mendez, Ghajarania & Perryman, 2002).

3.6 Synthesis of Results: Experimental Studies

3.6.1 Study Design & Demographic Information

Author(s) (Year)	Time Scale	Comparison or Control Group	Patient Group Characteristics	Patient Demographic Summary
Cohen et al. (2010)	Cross-sectional	Y	1 PCA, 5 healthy right handed adult participants	F, age 61 years, [no information provided on controls]
Meek et al. (2013)	Cross-sectional	N	4 PCA	3F, 1M, mean age 71.75 ± 6.13 years

Table 3.14: Study Design & Demographic Overview of Experimental Studies

Both of the articles used a combined cross-sectional case-study and experimental design. Cohen et al. (2010) tested one PCA patient and had a control group of five healthy, right-handed adult participants. Meek et al. (2013) tested 4 patients with PCA, and in contrast did not test any control subjects. Across both studies there was an approximately equivalent representation of female (n = 1) and male (n =3) patients with PCA. The mean age of PCA patients within the experimental studies was 69.60 years (SD = 7.16).

3.6.2 Diagnostic, Inclusion and Exclusion Criteria and PCA-Specific Symptoms Investigated

Author(s) (Year)	D. Criteria Defined	Basis of D. Criteria		Inclusion/ Exclusion Criteria Defined	Basis of Inclusion/ Exclusion Criteria		Target Symptoms Defined	Target Symptoms
		I	C		I	C		
Cohen et al. (2010)	Y	•	•	N			Y	Action-intentional spatial bias
Meek et al. (2013)	Y	•	•	Y	•	•	Y	Optic ataxia

Table 3.15: Diagnostic, Inclusion and Exclusion Criteria and PCA-Specific Symptoms Investigated of Experimental Studies
Key: D. = Diagnostic, Y = Yes, N = No, I = Imaging, H = histological, C = clinical/behavioural history or presentation, • = presence of diagnostic criteria

Both of the experimental studies, which were reviewed, presented detailed PCA diagnostic criteria based on both clinical behavioural history and at least two forms of brain imaging (including PET, MRI, and SPECT scans) (Cohen, Burtis, Cheol Kwan, Williamson & Heilman, 2010; Meek, Shelton & Marotta, 2013). Behavioural indicators of PCA were not defined by Cohen et al. (2010). The investigation by Meek et al. (2013) detailed characteristic symptoms, across cases, as intact memory and executive functioning with concurrent visual disturbances including: neglect, simultanagnosia, visual agnosia, constructional apraxia, elements of Gerstmann's syndrome, alexia and optic ataxia.

No inclusion or exclusion criteria were defined by Cohen and colleagues (Cohen, Burtis, Cheol Kwan, Williamson & Heilman, 2010). The second experimental study defined the inclusion criteria as a diagnosis of PCA from a local neurologist, based on cognitive and perceptual testing along with structural imaging (Meek, Shelton & Marotta, 2013).

The experimental studies under review investigated highly specific cognitive abilities within PCA. Cohen and colleagues investigated action-intentional spatial bias (Cohen, Burtis, Cheol Kwan, Williamson & Heilman, 2010), whereas

Meek and colleagues investigated optic ataxia, one of the triad of symptoms associated with Bálint's syndrome (Meek, Shelton & Marotta, 2013).

3.6.3 Outcome Measures, Tests of Visual Attention and Tests of Visuomotor Abilities

Author(s) (Year)	Validated outcome measure(s) used	Test of visual attention used	Test of visuomotor abilities used
Cohen et al. (2010)	Y	Y	Y
Meek et al. (2013)	N	N	Y

Table 3.16: Outcome Measures, Tests of Visual Attention and Tests of Visuomotor Abilities: Experimental Studies

Cohen and colleagues used line bisection and cancellation tasks in their assessment of visual attention (both of which have been validated for use in the assessment of disorders of visual attention, particularly for visual neglect) (Cohen, Burtis, Cheol Kwan, Williamson & Heilman, 2010). The cancellation task assessed both egocentric (failing to respond to stimuli on the left side of their body, e.g. on the left side of the page) and allocentric neglect (object-based, failing to respond on the left side of each stimulus) using a triangle cancellation paradigm where only triangles with gaps on their left or right side should be marked (Cohen et al., 2010). This article also included a test of visuomotor abilities, namely an assessment of directional akinesia (Cohen et al., 2010). This was assessed using a method initially reported by Heilman, Bowers & Watson (1983), involving the patient pointing with their finger or extended forelimb to a position in space perpendicular to their sternum. The mean deviation from the true midline was calculated and then used as a measure of directional akinesia (Cohen et al., 2010).

The investigation by Meek and colleagues included no assessments of visual attention (Meek, Shelton & Marotta, 2013). However, this paper did provide detailed methodological information on two visuomotor experiments using Efron blocks, which were designed to investigate optic ataxia under different viewing conditions (under different grasp instructions such a closed-loop,

immediate open-loop and delayed open-loop; and under different grasp distances, depth displaced from fixation) (Meek et al., 2013).

3.7 Review Update

A further database search exercise was conducted on the 12th February, 2019 in order to update the present review and to identify and summarise any relevant literature published after the initial search exercise in 2015.

The update database search was conducted following the same method as reported in Section 3.1. The initial update search identified 891 newly published articles, of which 53 were duplicates. Therefore, 838 references were screened in order to identify those which met the inclusion criteria for review. Following the screening exercise 23 papers were identified for second stage screening. After the second stage of screening a total of 6 papers were subsequently identified as meeting the full inclusion criteria for review. Summary tables and further discussion on the results of the data extraction process are presented in the sections below.

For simplicity of presentation, the review update papers which were analysed and reported in the following section are presented below:

- Glazer, Saadatpour, Doty, & Heilman (2017)
- Li et al. (2018)
- Nagaratnam, Cheuk & Nagaratnam (2015)
- Neitzel et al. (2016)
- Peng et al. (2016)
- Zilli & Heilman (2015)

3.7.1 Study Design & Demographic Information

Author(s) (Year)	Time Scale	Single or Multiple Case Study	Comparison or Control Group	Patient Group Characteristics	Patient Demographic Summary
Glazer et al. (2017)	Cross-sectional	Single	N	1 PCA	M, age 70 years
Li et al. (2018)	Cross-sectional	Multiple	Y	21 PCA	PCA: 10F, 8M, mean age 57.5 ± 6.1 years EOAD: 12F, 8M, mean age 52.5 ± 7.3 years Controls: 12F, 8M, mean age 52.5 ± 7.7 years
Nagaratnam et al. (2015)	Cross-sectional	Single	N	1 PCA	M, 79 years
Neitzel et al. (2016)	Cross-sectional	Multiple	Y	12 PCA	PCA: 5F, 7M, mean age 64.2 years ± 7.5 years Controls: 6F, 6M, mean age 64.9 ± 2.5 years
Peng et al. (2016)	Cross-sectional	Multiple	Y	16 PCA	PCA: 7F, 9M, mean age 55.8 ± 6.5 years tAD: 7F, 6M, mean age 59.9 ± 8.2 years Controls: 8F, 7M, mean age 57.6 ± 7.3 years
Zilli & Heilman (2015)	Cross-sectional	Single	N	1 PCA	F, age 64 years

Table 3.17: Study Design & Demographic Overview of Review Update Papers
Note: EOAD = early onset Alzheimer's disease, tAD = typical Alzheimer's disease.

Of the papers included in the review update, half (n = 3) were single case studies (Glazer, Saadatpour, Doty, & Heilman, 2017; Nagaratnam, Cheuk & Nagaratnam, 2015; Zilli & Heilman, 2015), and half (n = 3) were multiple case studies, utilizing control and/or clinical comparison groups and a mean PCA cohort of 16.3 (Li et al., 2018; Neitzel et al., 2016; Peng et al., 2016). All of the studies analysed in this update utilised a cross-sectional approach which is in

contrast with the older studies presented in the main body of this systematic review, where longitudinal and retrospective designs were also used. This may suggest that contemporary research on PCA tends towards cross-sectional research designs.

3.7.2 Diagnostic, Inclusion and Exclusion Criteria and PCA-Specific Symptoms Investigated

Author(s) (Year)	D. Criteria Defined	Basis of D. Criteria		Inclusion / Exclusion Criteria Defined	Basis of Inclusion / Exclusion Criteria		Target Symptoms Defined	Target Symptoms
		I	C		I	C		
Glazer et al. (2017)	N			N			Y	Vertical neglect
Li et al. (2018)	Y	•	•	Y	•	•	N	
Nagaratnam et al. (2015)	N			N			N	
Neitzel et al. (2016)	Y	•	•	Y	•	•	Y	Simultan-agnosia
Peng et al. (2016)	Y	•	•	Y		•	N	
Zilli & Heilman (2015)	Y	•		N			Y	Allocentric spatial neglect

Table 3.18: Diagnostic, Inclusion and Exclusion Criteria and PCA-Specific Symptoms Investigated of Review Update Papers
Key: D. = Diagnostic, Y = Yes, N = No, I = Imaging, C = clinical/behavioural history or presentation, • = presence of diagnostic criteria

The single case study papers included in the review update all failed to report any diagnostic or inclusion/exclusion criteria, although the investigation by Zilli and Heilman notes some imaging characteristics of the PCA patient studied (Glazer, Saadatpour, Doty, & Heilman, 2017; Nagaratnam, Cheuk & Nagaratnam, 2015; Zilli & Heilman, 2015). The multiple case study papers all reported using prior published clinical criteria for the diagnosis of PCA, although each paper used different criteria (Li et al., 2018; Neitzel et al., 2016; Peng et al., 2016). Li and others used the AAIC International Working Group clinical criteria for PCA, in addition to imaging from CT, MRI, PET and SPECT methodologies (Li et al.,

2018; Crutch et al., 2013). Neitzel and colleagues applied published criteria for PCA as reported in Mendez, Ghajarania & Perryman (2002) (Neitzel et al., 2016). Patients were additionally screened for AD biomarkers based on amyloid-PET and CSF screening, and clinical diagnosis was confirmed via multidisciplinary team consensus (Neitzel et al., 2016). The investigation by Peng et al. reported that PCA patients included in their study fulfilled previously proposed clinical diagnostic criteria (Wang et al., 2015), and that the clinical diagnosis was supported by follow-up assessments (Peng et al., 2016).

The exclusion criteria reported in the multiple case studies varied, although was generally homogeneous in that patients were excluded if there was any evidence of any other neurological disorder (Li et al., 2018; Neitzel et al., 2016; Peng et al., 2016). For example, Li and collegeues report that patients were excluded if a clear history of white matter disease (including white matter lesions), other neurological diseases, or one of a range of other neurological disorders was evident (Li et al., 2018). Neitzel et al. develop these exclusion criteria slightly and report that evidence of vascular pathology (identified via white matter hyperintensities) would also lead to a patient's exclusion from participation (2016). Peng and colleagues provided more general exclusion criteria than the other multiple case study papers and note that patients were excluded who exhibited early symptoms of myoclonus, extrapyramidal motor signs, and hallucinations: in other words, if there was evidence of other neurological conditions) (Peng et al., 2016).

The PCA-specific symptoms under review by each article varied. Two of the multiple case study papers did not identify any target symptoms of interest, but instead aimed to provide an overview of performance on a range of neuropsychological measures in comparison with patients with other neurodegenerative diseases – including EOAD and tAD – and healthy controls (Li et al., Peng et al., 2016). The additional multiple case study paper investigated symptoms of simultanagnosia (SA) in their cohort of patients (Neitzel et al., 2016). Two of the single case studies investigated visual neglect,

with Glaser and colleagues reporting a case of vertical neglect, and Zilli and Heilman reporting a case of allocentric visual neglect (Glazer, Saadatpour, Doty, & Heilman, 2017; Zilli & Heilman, 2015). One single case paper investigated the presence of optic ataxia in the PCA patient studied (Nagratnam et al., 2015).

3.7.3 Outcome Measures, Tests of Visual Attention and Tests of Visuomotor Abilities

Author(s) (Year)	Validated outcome measure(s) used	Test of visual attention used	Test of visuomotor abilities used
Glazer et al. (2017)	Y	N	Y
Li et al. (2018)	Y	N	Y
Nagaratnam et al. (2015)	N	Y	Y
Neitzel et al. (2016)	Y	Y	N
Peng et al. (2016)	ND	Y	Y
Zilli & Heilman (2015)	Y	Y	Y

Table 3.19: Outcome Measures, Tests of Visual Attention and Tests of Visuomotor Abilities: Review Update Papers
Note: ND = not determined.

It was not possible to determine whether the attentional and visuomotor measures used by Peng and colleagues were validated or standardized versions, as no detail was provided on the specifics of these assessments: instead the paper reports that "a battery of neuropsychological tests designed to assess … attention … [and] visuospatial ability … were also used" (Peng et al., 2016, p. 2). Further, the authors note that components of Gerstmann and Bálint-Homes syndromes were assessed using "unstandardized tasks" during neurological and neuropsychological examinations (Peng et al., 2016, p.2).

Similarly, the single case study reported by Nagratnam and colleagues did not provide any detail on the neuropsychological tests used (and thus, it was not possible to establish whether these were validated measures) (Nagaratnam, Cheuk & Nagaratnam, 2015). However, a test for OA was described which involved touching target items on a picture, and finger tracing the outline of a map (Nagratnam et al., 2015). Although certainly not considered the 'gold standard' method of assessing OA, similar methods of assessment of OA have been reported previously. The multiple case study reported by Li and colleagues

included a range of validated assessments, intended to provide an overall neuropsychological performance profile in order to compare the clinical groups (Li et al., 2018). These included the Bells Cancellation Test (used in the assessment of disorders of visual attention, such as neglect), Navon figures (typically used to assess for the presence of SA), and the posterior neuropsychological battery (which includes a test of visual neglect) (Kas et al., 2011; Li et al., 2018).

Neitzel and colleagues describe a method for the assessment of SA taken from Luck & Vogel (1997), where letters are displayed simultaneously in the form of columns and participants are required to report as many letters as possible (Neitzel et al., 2016). The duration of exposure to the letters was manipulated in this paradigm (short, medium, and long) in order to determine whether processing speed is implicated in presentations of SA (Neitzel et al., 2016). In tandem, SA was additionally screened using the BORB Overlapping Figures Task (Riddoch & Humphreys, 1993), two subtests from the Visual Object and Space Perception Battery known to be sensitive to SA (dot counting and position discrimination task) (Warrington & James, 1991) and the computerized simultaneous-perception task (SPT), all of which have been validated for use in screening for SA (Finke et al., 2007; Neitzel et al., 2016).

The single case investigation by Glaser and colleagues detailed various bisection tasks used in the assessment of the patient's vertical neglect; namely horizontal and vertical line bisection tasks and an 'open-box' cancellation task (where the participant is required to mark open boxes, which allows for the assessment of allocentric and egocentric neglect) (Glazer, Saadatpour, Doty, & Heilman, 2017). The open-box cancellation task was also utilized by Zilli and Heilman (in order to test for stimulus-centered allocentric visual neglect) in addition to a vertical bisection task and Luria Alternating Squares and Triangles test, both intended to measure aspects of visual attention (Luria, 1970; Zilli & Heilman, 2015).

3.8 Additional Analyses

3.8.1 Neuropsychological Assessments Reported in PCA

At the first stage of review a total of 274 articles specific to PCA were removed from further analysis as they did not meet criteria for inclusion in the main review.

In order to gain a qualitative overview of the neuropsychological assessments used in the assessment of PCA, the papers were screened by hand to extract information regarding reported assessments. Information on which neuropsychological assessments (if any) had been used was extracted from the methodology section of each paper.

It was possible to extract these data from 30 papers, in addition to the 10 papers which were systematically reviewed. The majority of papers were not eligible for data extraction of this kind. Table 3.20, below, provides an overview of the 244 papers for which data on validated neuropsychological assessments was not possible to extract and the reason why this was not possible.

Reason Code	Frequency
Imaging methodology only, NNA	60
Histology methodology only, NNA	54
Meta-analysis or review methodology only, NNA	37
Experimental paper, NNA	28
No text available	18
Not available in English	11
No methodological details available (e.g. poster presentation)	11
Not specific to PCA	10
Genetic analysis methodology only, NNA	9
Non-validated neuropsychological assessment (e.g. the paper reports an experiment in which a new NA has been designed)	6
Total:	244

Table 3.20: Qualitative Assessment of Validated Neuropsychological Assessments in PCA Papers Not Applicable for Systematic Review: Reason that Data Were Not Extractable

Note: NNA = no neuropsychological assessment, NA = neuropsychological assessment.

A database was created with all reported neuropsychological assessments from the 10 papers which were systematically reviewed in addition to the 30 papers which were not systematically reviewed (total n = 40). Assessments reported in more than two articles (i.e. with a frequency of greater than two) are presented in Table 3.21, below. An elaborative table including all reported, validated neuropsychological assessments and their frequency is presented in Appendix 3.

Assessment Category	Test Name	Frequency
1. General Dementia Screen		
	Clinical Dementia Rating Scale	4
2. Psychiatric & Quality of Life		
	*	
3. General Cognitive Abilities		
	Mini Mental State Examination (MMSE)	21
	Kolkata Cognitive Battery	18
	Wechsler Adult Intelligence Scale (WAIS)	5
	Seoul Neuropsychological Screen Battery (SNSB)	4
	The Cognitive Estimation Test (CET)	4
4. Memory		
	*	
5. Executive Functions		
	Clock Drawing Test – Copying (CLOX-2)	5
	Clock Drawing Test – Free Drawn (CLOX-1)	4
	Trail Making Test (TMT) - A	4
	CERAD – Verbal Fluency Subtest	4
6. General Early Visual Functions		
	The Visual Object and Space Perception Battery (VOSP)	4
7. General Late Visual Functions		
	Rey-Osterriech Complex Figure Test (ROCF)	4
	Hooper Visual Organisation Test (VOT)	3
	VOSP – Number Location Subtest	3
8. Visual Attention & Neglect		
	Line Bisection	4
9. Visual Agnosia		
	Boston Naming Test (BNT)	7
	Boston Naming Test - Short Form Subtest	4
10. Simultanagnosia		
	VOSP – Dot counting Subtest	3
	Navon Figure Test – Global Shape Recognition	3
11. Speech & Language		
	Token Test – Short Form	3
12. Numeracy		
	*	
13. Apraxia		
	*	

Table 3.21: Qualitative Assessment of Validated Neuropsychological Assessments in PCA Papers: Tests Reported with a Frequency of > 2.
Note: Many of these tests could be assigned multiple categories, therefore for simplicity tests have been organised into categories which they are most commonly associated with.
* For this category, no tests were reported with a frequency of > 2. See Appendix 3 for a complete list.

Categories of assessment reported above should be interpreted cautiously, as a great deal of the tests listed could be semantically organised under multiple classifications. However, for simplicity, the assessments have been classified according to the most relevant cognitive domain category with respect to the assessment of PCA patients.

From this summary it can be seen that the only validated assessment reported in more than half of studies screened was the MMSE (52.5% frequency, n = 21), a test of general cognitive abilities. The second most frequently reported assessment was The Kolkata Cognitive Battery (also a test of general cognitive abilities), reported with a frequency of 45% (n = 18).

There appears to be little continuity across articles on the other categories of assessment, with the level of assessment continuity across studies reaching a maximum of 17.5% (visual agnosia: Boston Naming Test, n = 7), and the next most frequently reported assessment at just 12.5% (executive functions: CLOX-2, n = 5).

For around 31% (n = 4) of categories defined during the screening process, assessments were not reported with a frequency greater than 2 (psychiatric & quality of life, memory, numeracy, and apraxia). This indicates a low level of consistency for PCA-specific articles on the use of validated assessments directly investigating these categories.

This qualitative overview serves to illustrate the lack of methodological agreement in terms of validated neuropsychological assessments used across studies on PCA at the time of writing.

3.8.2 Presenting Symptoms in PCA

In order to obtain further insight into the most commonly reported symptoms of PCA across the 10 articles systematically reviewed – information on reported

presenting symptoms, and any symptoms reported after presentation (such as at additional assessment time points) were extracted. This was intended to provide information on what the most common presenting symptoms of PCA are, as well as providing a view on what the most frequently reported later symptoms are (which are not common presenting symptoms).

There was a great deal of variation across the 10 articles studied in terms of the number of PCA patients within the sample, and the level of detail in which symptoms were reported, with case study articles providing the greatest level of detail.

In order to account for variations in patient numbers, presenting 'first wave' symptoms and later 'second wave' symptoms are reported in terms of the frequency of papers in which they appear, rather than the number of patients reported to have the symptom.

Table 3.22, below, presents the 10 most frequently reported first wave symptoms, and the 10 most frequently reported second wave symptoms which are unique (i.e. which do not appear in the 10 most frequent first wave symptoms).

First Wave		Second Wave	
Symptom	**Frequency**	**Symptom**	**Frequency**
Visual impairments	7	Agraphia	4
Reading difficulties	6	Bálint's Syndrome	4
Face recognition deficits	5	Right/left discrimination	4
Environmental agnosia	4	Speech difficulties	4
Object agnosia	4	Alexia	3
Blurred vision	3	Attention deficits	3
Cognitive/intellectual impairment	3	Comprehension deficits	3
Dressing apraxia	3	Deficits in constructional abilities	3
Dysarthria	3	Gerstmann's Syndrome	3
Acalculia	2	Mental state deterioration	3

Table 3.22: The 10 Most Frequently Reported First and Second Wave Symptoms in Systematic Review Articles Studied (10 papers in total).

It is unsurprising to find that the most frequently reported first wave symptom is that of visual impairments (not otherwise specified), given the involvement of the occipital cortex at the start of the PCA disease process. What is perhaps more interesting is the finding that environmental agnosia is a common symptom within this population. Further research could address what the cause of this symptom is – whether it is a memory or a visual recognition deficit – and therefore lead to recommendations to aid these individuals. Symptoms such as face recognition deficits and object agnosia hint at ventral stream impairment in the early stages of the disease, whereas deficits like dressing apraxia relate to dorsal stream damage and possible motor impairments. Dysarthria is an interesting symptom to find so frequently reported, and may suggest more left hemisphere involvement than is typically reported, as speech articulation is generally lateralised to the left-hemisphere (Urban et al., 2006).

Second wave symptoms are more diffusely reported, with a multitude of additional symptoms noted across papers. The most commonly reported symptoms across the 10 papers included agraphia, constructional abilities and right/left discrimination difficulties (suggestive of motor and attentional

difficulties), Bálint's and Gerstmann's syndrome, speech difficulties, alexia, problems with attention and concentration (perhaps suggestive of more frontal involvement), and deterioration in mental state.

Symptoms which appear to be persistent throughout the course of PCA and which therefore may be helpful indicators of the presence of PCA, largely disregarding the time point of assessment, are reported in Table 3.23, below. These symptoms were reported as presenting symptoms, and were additionally reported at a later assessment. In total, 19 symptom types were common to both presenting and follow-up symptom reporting in the 10 papers reviewed.

Symptom	First Wave Frequency	Second Wave Frequency
Visual impairments	7	1
Reading difficulties	6	4
Environmental agnosia	4	4
Object agnosia	4	2
Dressing apraxia	3	4
Cognitive/intellectual	3	1
Visuospatial deficits	2	3
Object localisation deficits	2	3
Acalculia	2	2
Driving difficulties	2	1
Right/left discrimination	1	4
Gerstmann's Syndrome	1	3
Memory deficits	1	2
Anxiety/depression	1	2
Activities of daily living	1	2
Deterioration in executive functions	1	2
Gait problems	1	1
Spelling difficulties	1	1
Word finding difficulty	1	1

Table 3.23: Symptoms Common to Both First and Second Wave Reporting in PCA

This overview of symptoms offers an insight into the everyday deficits which are associated with the pattern of brain atrophy observed in PCA. Visual impairments and difficulties with reading are among the most common first wave symptoms, and reading in particular remains a commonly reported second wave symptom. It is unsurprising, therefore, that so many patients first attempt to address these issues by seeing an optician (Shakespeare, Ryan,

Petrushkin & Crutch, 2012). Suggestions for future research from these findings are presented in Section 3.8.2 of this chapter.

3.9 Discussion

3.9.1 Summary of Results

The majority of papers under review were case studies, with a small number of group comparison and experimental studies. The number of PCA patients reported on ranged from 1-17, with group comparison studies generally recruiting more patients, and case study and experimental papers recruiting up to five patients. Therefore, at the time of writing, investigations into visual attention and visuomotor symptoms in PCA generally report on small sample sizes of patients – most likely a reflection on the rarity of the disorder and the poor diagnostic criteria available for PCA. An approximately equivalent representation of males and females was observed across all studies. The mean age of PCA patients across all studies ranged from 59-69 years.

Regarding the diagnostic, inclusion and exclusion criteria, the criteria used were generally rather heterogeneous. This may reflect the fact that, as yet, there is no universally agreed clinical or imaging diagnostic definition of PCA (Crutch et al., 2017). Likewise, no exclusion criteria were listed for any study under review, and those studies which detailed inclusion criteria used clinical behavioural indicators, imaging correlates, or a combination of both measures (Meek, Shelton & Marotta, 2013; Mendez, Ghajarania & Perryman, 2002; Nagratnam, Nagratnam, Jolley, & Ting, 2001). Given the highly typical pattern of atrophy observed in patients with PCA, and the associated indicative visuoattentional and visuomotor symptoms, a combined approach to identifying patients with PCA for inclusion in studies is likely to be the most robust until a clearer consensus can be reached on the neuropsychological hallmarks of PCA, and until sensitive diagnostic tests can be developed in order to reliably identify these symptoms.

The symptoms studied varied widely, with some very specific to PCA and others more general (perhaps seeking a more general overview of cognitive abilities within the sample). This may also be a reflection of the poorly defined diagnostic criteria for PCA so far – and the fact that these articles are very exploratory in nature given the relative rarity of the disease and the limited research investigating it so far.

There was a limited use of tests specific to visual attention within the case study papers (Ardila, Rosselli, Arvizu, & Kuljis, 1997; Caixeta, Taleb, Ghini, Dias Soares, de Melo Caixeta, & Vargas, 2013), and only half of case study articles assessed visuomotor abilities (Caixeta et al., 2013; Nagratnam, Nagratnam, Jolley, & Ting, 2001; Rogelet, Delafosse & Destee, 1996). Moreover, the methodology of these visuomotor assessments was not clearly reported. Both group comparison studies used validated assessments and both included more than two assessments of visual attention (Aresi & Giovagnoli, 2009; Mendez, Ghajarania & Perryman, 2002). Only one group-comparison study included tests which could be classified as visuomotor, but these assessments relied on rather subjective results (Mendez, Ghajarania & Perryman, 2002). The first experimental study used validated assessments of visual attention and included a test of visuomotor ability in the form of directional akinesia (Cohen et al., 2010). The second experimental study did not use a test of visual attention but did report, in-depth, a methodology applied to the PCA patients in order to investigate optic ataxia – a symptom associated with deficits in visuomotor performance (Meek, Shelton & Marotta, 2013).

The articles included in the review update appeared to present a more homogenous picture than the originally reviewd articles, with more papers reporting the application of published diagnostic criteria for PCA (Li et al., 2018; Neitzel et al., 2016; Peng et al., 2016), and a greater proportional frequency of validated assessments of visual attention and visuomotor abilities being reported (Glazer, Saadatpour, Doty, & Heilman, 2017; Li et al., 2018; Neitzel et al., 2016; Zilli & Heilman, 2015). This may represent a shift in the research

literature on PCA towards more organized and better-informed research, with a greater frequency of targeted assessments of PCA-specific symptoms.

3.9.2 Conclusions & Suggestions for Future Research

From this review it is apparent that there has been relatively little attempt to formally typify the characteristic visouattentional and visuomotor symptoms frequently reported in patients with PCA. The studies which did so, as reported within this review, showed little methodological consistency. Likewise, reporting of results and statistical approaches to analysis are variable and often absent from reports. Given that PCA is a disease for which – even decades after its identification by Benson and colleagues – no formal diagnostic classifications are available, emphasis should be given to developing standard diagnostic criteria for PCA which can be used as a platform for future research (Benson, Davis, & Snyder, 1988; Crutch et al., 2012; Crutch et al., 2017). A recent paper by Crutch and colleagues (2017) has provided a good framework for classifying and identifying PCA, but further research is required to untangle some of the more general symptom labels (such as 'space perception disorder') into individual neurobehavioural symptoms which can then be screened for (such as optic ataxia and neglect).

The additional stream of analysis reported within this systematic review addressed the symptoms which are commonly reported across the PCA papers reviewed. Deficits in vision are among the most frequently reported symptoms, a rather unremarkable finding given the pattern of atrophy associated with PCA. However, the results of this brief overview highlight some behavioural symptoms which appear to be commonly reported across the course of the disease and which may be useful flags to identify PCA when it may otherwise go undiagnosed. Patients with PCA frequently consult their optician when they first notice changes in their visual abilities (Shakespeare, Ryan, Petrushkin & Crutch, 2012). Occasionally the optician may be alerted to the possibility of cortical visual dysfunction, in which case patients would be referred to a neurologist,

but often patients may have relatively normal eye exam performance and therefore are not assessed further (Shakespeare et al., 2012). This may contribute to the lengthy delays observed for PCA patients to receive a correct diagnosis from symptom onset (Crutch et al., 2013, 2012). Given the generally intact insight observed in PCA patients until late in the disease course, it may be possible for a brief questionnaire-style screening tool to be developed which quantifies the level of difficulty the individual finds not only with vision, but also with other activities which appear to be common symptoms of PCA (like environmental agnosia, object agnosia, and dressing apraxia). Such a screen could therefore be used as part of an eye examination for those patients who complain of symptoms which seem incompatible with the results of the eye examination, and thus potentially expedite diagnosis.

4. Screening Data

4.0 Introduction

4.0.1 Background to Dementia Screening

The WHO estimate the total number of new cases of dementia worldwide to be almost 7.7 million per year - or one new case every 4 seconds (World Health Organization, 2012). Despite these alarming statistics there exists a 'diagnosis gap', referring to those individuals living with dementia who have not received a diagnosis (Prince, Comas-Herrera, Knapp, Guerchet & Karagiannidou, 2016). Based on analyses of health systems with respect to dementia, estimates suggest that between one third to 75% of individuals with dementia may not receive a diagnosis (Feldman, Wilcock, Thuné-Boyle & Iliffe, 2017: Bannerjee, 2015; Russell et al., 2013). Therefore, the result of this gap is that too few people are being diagnosed correctly with dementia, or are not being diagnosed early enough (Menon & Larner, 2011). Inclusion of dementia as a chronic condition requiring special attention within the Quality and Outcomes Framework of the UK General Practitioner (GP) contract has resulted in primary care physicians being more positive about diagnosing dementia early (Menon & Larner, 2011). Longitudinal evidence suggests changes in national policy relating to the prioritization of dementia has had a positive effect on diagnosis rates and quality of drug treatments, with rates of diagnosis doubling over a 10 year period from 2005-2015, and rates of the use of potentially harmful antipsychotic medications halving within this time (Donegan et al., 2017). There are a limited number of pharmacotherapeutic agents available which are typically used in the management of dementias (Raina et al., 2008; Schwarz, Froelich & Burns, 2012). These include cholinesterase inhibitors (including donepezil, galantamine, rivastigmine, and tacrine), which operate by increasing levels of acetylcholine (a neurotransmitter involved in cognition), as well as drugs which operate to prevent excess stimulation of the glutamate system (implicated in learning and memory) (Raina et al., 2008; Schwarz, et al., 2012).

Guidelines published by the National Institute for Health and Clinical Excellence in collaboration with the Social Care Institute for Excellence (NICE, 2018) highlight the importance of early identification of dementia, suggesting rapid referral of those individuals showing signs of mild cognitive impairment (MCI), which is considered an intermediate stage in cognitive function between normal ageing and dementia (NICE, 2018; Petersen, 2011). Screening of patients to determine cognitive deficits is a vital requirement both for the initial diagnosis of a neurodegenerative disease (NDD) and to monitor disease progression following diagnosis. The gold standard for diagnosis within dementia is neuropathology, therefore a true diagnosis of the pathology underlying the dementia is often not possible until autopsy (Philips, Walters, Biju & Kuruvilla, 2016; Fox, Lafortune, Boustani & Brayne, 2013). The challenge of developing valid and reliable screening measures for dementia lies within the fact that dementia is not a disease but a syndrome, clinical features of which are all continuous – varying between individuals – and are affected by a plethora of additional factors (Fox et al., 2013). The newest diagnostic criteria for dementia (among other disorders), within the Diagnostic and Statistical Manual of Mental Disorders (5th Edition) (DSM-5), are considered controversial due in part to perceived over-influence of the pharmaceutical industry on classifications, and on 'medicalising' behaviours and moods which may not be particularly extreme, such as with the newly defined 'mild neurocognitive disorder', leading to so-called "diagnostic inflation" (Frances & Widinger, 2012, p.122). Such controversy creates an additional hurdle to detection and diagnosis as it undermines the legitimacy of the DSM-5 as a diagnostic tool. Inaccurate diagnostic criteria undermine research and theory, and create an unnecessary road-block to the development of more accurate criteria, and indeed to better treatments (Wakefield, 2016).

Additionally there may be resistance to diagnosing individuals with MCI or dementia for whom such a diagnosis would be considered to do "more harm than good" (Fox, Lafortune, Boustani & Brayne, 2013, p.e510), due to the tools

available for identifying the early cognitive changes associated with dementia and AD currently outpacing the therapeutic options for these patients (Fox et al., 2013; NICE, 2018). As yet there are no meaningful disease-modifying drug treatments available for dementia, and lifestyle adjustments such as reducing cardiovascular risk factors with respect to vascular dementia have arguably little overall benefit (Philips, Walters, Biju & Kuruvilla, 2016). Additionally, the stigma associated with a diagnosis of dementia as well as the risk associated with false positives (unnecessary treatments possibly leading to harm, increased financial burden to health services, and risk of under-treatment of differential diagnoses such as depression) add to the consensus among some that early diagnosis only brings "stress and fear" (Hill & Walton, 2013, p.8; Ladds, Ryan & Mahtani, 2013). However, receiving a formal diagnosis of dementia allows the patient and their family to be more actively involved in decisions pertaining to them. Advantages cited from early diagnosis of dementia include the ability to plan support in terms of treatment and future care needs, opportunities to make legal arrangements and to make financial decisions, reduced uncertainty and time to come to terms with their diagnosis, as well as offering the opportunity to pursue genetic counselling (Cullen, O'Neill, Evans, Coen & Lawlor, 2007; Iliffe, Manthorpe & Eden, 2003).

Despite the ethical and practical implications of diagnosing more individuals with dementia, there remains a demand for increasingly sensitive and cost-effective diagnostic tests. Early detection of dementia facilitates better understanding and treatment of symptoms, enables both financial and care planning, allows greater opportunity for participation in research programmes and may improve medication adherence (Alzheimer Europe, 2009). Many of the well-established cognitive screens, widely used as supplementary diagnostic tools, are less sensitive diagnostically when dealing with younger age ranges outside of those most commonly associated with dementia (Philips, Walters, Biju & Kuruvilla, 2016). Memory is the most tested function but will not identify all cases (Philips et al., 2016). Likewise, shorter-form tests are less sensitive at identifying rarer forms of dementia such as the frontal dementias (Philips et al.,

2016). In addition, it is claimed that many screening tests have not been appropriately validated in the populations for which they are intended which further limits their diagnostic validity (Philips et al., 2016; Cullen, O'Neill, Evans, Coen & Lawlor, 2007). An attempt should not be made to seek a "one size fits all" solution for cognitive screening for dementia as less common presentations of dementia, and unusually early presentations of the disease, can easily be missed (Cullen, O'Neill, Evans, Coen & Lawlor, 2007, p.795).

4.0.2 Screening for PCA

PCA in particular continues to be something of an enigma for medical professionals, as described in the general introduction of this thesis, and as patients with PCA are typically younger at the age of onset and have relatively preserved memory at the earliest stages of the disease, these patients are at even greater risk of not being accurately diagnosed. The most frequently reported symptoms associated with PCA are Bálint's syndrome (optic ataxia, oculomotor apraxia and simultanagnosia), visual field deficits, alexia, Gerstmann's syndrome (right-left disorientation, finger agnosia, acalculia, and agraphia), and visual agnosia (Benson, Davis & Snyder, 1988; Tang-Wai et al., 2004; McMonagle, Deering, Berliner & Kertesz, 2006). In addition, patients with PCA typically have preserved insight which, bluntly put, means that they are aware of their disease and what the consequences of it are, at least in the early stages, which often leads to anxiety and depression within this patient group (Benson, Davis & Snyder, 1988; Tang-Wai et al., 2004; McMonagle et al., 2006).

PCA is generally neglected in any recommendations for cognitive screening for dementia, with most recommendations suggesting tests which, while accurate at identifying more typical presentations, may not target the domains in which observed deficits are commonly associated with PCA, particularly in the early stages (Bossers, van der Woude, Boersma, Scherder & van Heuvelen, 2012; Milne, Culverwell, Guss, Tuppen & Whelton, 2008). For example, many cognitive screening tests used in dementia over-emphasize the domain of memory,

neglecting other domains like language, executive functions, praxis and vision (Cullen, O'Neill, Evans, Coen & Lawlor, 2007). Patients with PCA typically experience erosion of skills in visuospatial, visuoperceptual, numeracy and literary abilities (Beh et al., 2015). These symptoms belong to domains not commonly assessed by popular cognitive screening measures used in dementia, thus further prolonging the time taken to receive the correct diagnosis for these patients or possibly resulting in patients being misdiagnosed or not diagnosed at all (Beh et al., 2015; Crutch et al., 2013; Crutch et al., 2012).

Prognosis and management of PCA are different from prognosis and management for AD, therefore there is a need to improve screening for this rarer form (Charles & Hillis, 2005). Although PCA, as a clinical syndrome, has been recognised for more than two decades, only recently has a formal attempt been made to create a classification framework for the disease (Crutch et al., 2012; Crutch et al., 2017).

The formal classification framework for PCA, developed by Crutch et al. (2017) has provided three levels of classification of this condition. The first level is concerned with the core clinical and cognitive features that describe the PCA syndrome (Crutch et al., 2017). Level two establishes whether the presentation is of pure PCA or whether the individual meets criteria both for PCA and for an additional neurodegenerative syndrome. The third level provides a disease-level description relating to the pathophysiological biomarker evidence for PCA (Crutch et al., 2017). Most pertinent to this study are the definitions provided in classification level 1. Figure 4.1 and Figure 4.2 (below) present detail on the findings of an online survey of group members as well as classification framework 1 as presented by Crutch and colleagues (2017).

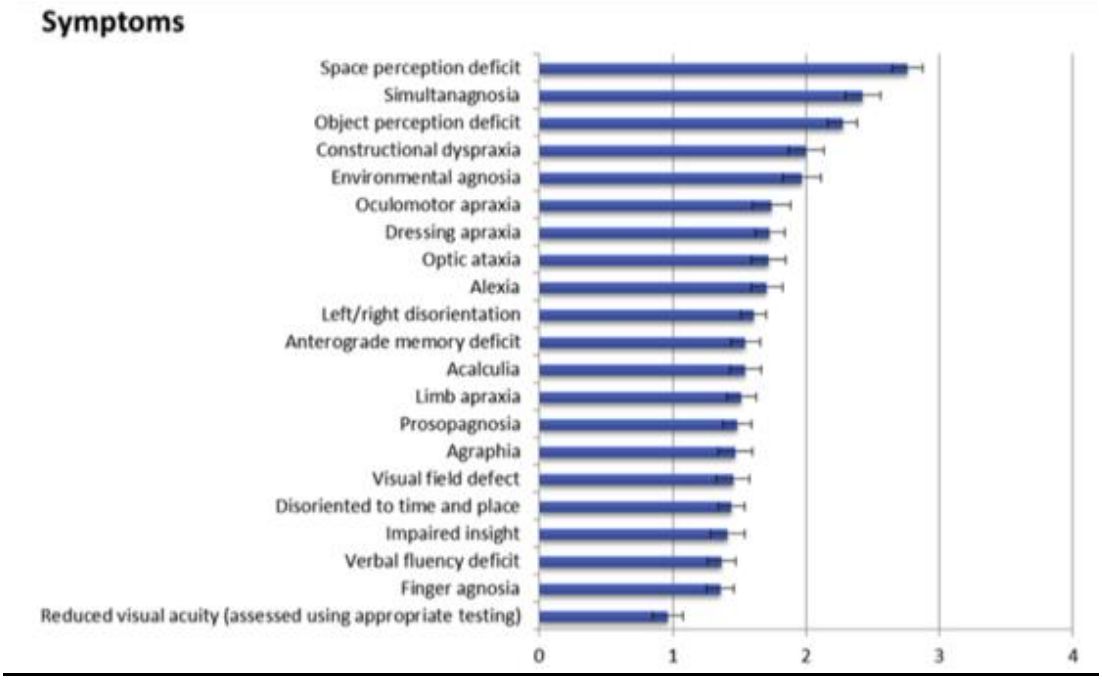


Figure 4.1: Online survey results from working party group members on clinical symptoms in PCA, taken from Crutch et al., 2017.

The results presented in Figure 4.1, above, are the mean and standard error ratings of clinical presentation symptoms of PCA. These were compiled from PCA working party and Atypical Alzheimer's Disease and Associated Disorders Professional Interest Area members, 36 of whom responded to an online survey in which they were asked to estimate the frequency of symptoms (among other features) (Crutch et al., 2017). Responses were given on the following scale: never seen (0%, point 0), rare (0-25%, point 1), common (25-75%, point 2), very frequent (75-100%, point 3), always present (100%, point 4) (Crutch et al., 2017). The results of this survey were used as a basis on which to draft the subsequent consensus classification, discussed in detail below.

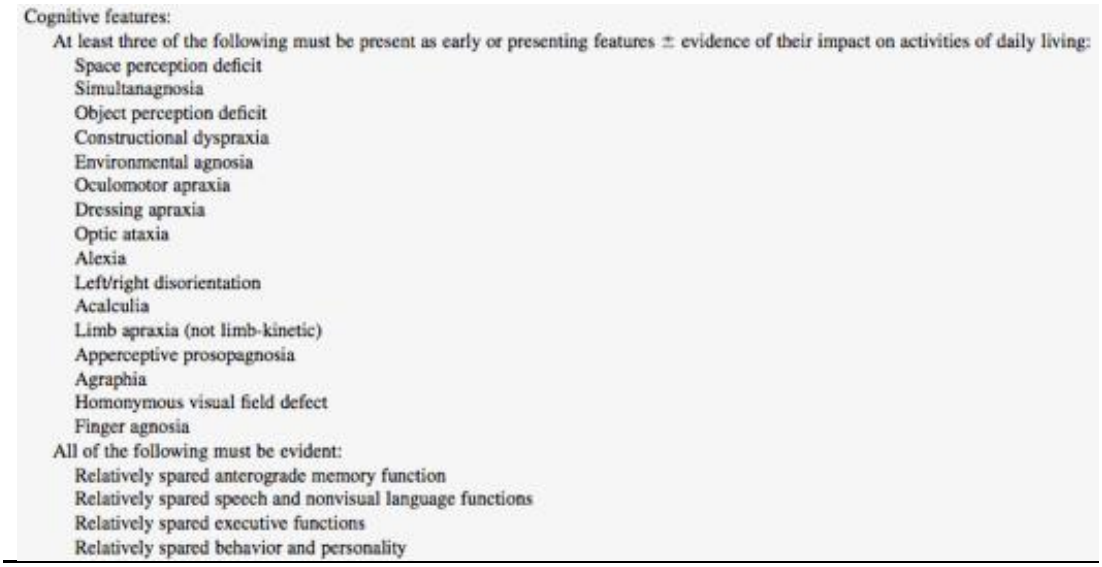

Cognitive features:
At least three of the following must be present as early or presenting features ± evidence of their impact on activities of daily living:
Space perception deficit
Simultanagnosia
Object perception deficit
Constructional dyspraxia
Environmental agnosia
Oculomotor apraxia
Dressing apraxia
Optic ataxia
Alexia
Left/right disorientation
Acalculia
Limb apraxia (not limb-kinetic)
Apperceptive prosopagnosia
Agraphia
Homonymous visual field defect
Finger agnosia
All of the following must be evident:
Relatively spared anterograde memory function
Relatively spared speech and nonvisual language functions
Relatively spared executive functions
Relatively spared behavior and personality

Figure 4.2: Classification Level 1: Cognitive Features of the PCA clinic-radiological syndrome, taken from Crutch et al., 2017.

The most frequently reported symptom, and the first cognitive feature listed within classification framework 1 (Figure 4.2) is that of 'space perception deficit'. This symptom is not defined by the authors of the paper, but is assumed to include neglect, a symptom reported historically in studies of PCA, but likely to be dramatically underestimated given the specificity of tests required to assess it (Mendez, Ghjarania & Perryman, 2002; Rogelet, Delafosse & Destee, 1996; Andrade et al., 2010). Neglect is generally defined as a failure to perceive or respond to stimuli on one side of space (Driver & Vuilleumier, 2001). Neglect has been characterised in various ways within the literature, as a disorder of attention, of perception, or indeed as an intentional, premotor or representional disorder (Halligan & Marshall, 1994). Deficits in attention, intention, global or local processing, spatial memory and mental representation may all contribute to a clinical presentation of neglect (Halligan et al., 2003). A detailed discussion

on neglect, and in-depth analysis of assessments of neglect presented to the patients within this sample are presented in Chapter 5.

Simultanagnosia represents the second most common symptom associated with PCA, according to the framework presented by Crutch et al. (2017). It forms one of the triad of symptoms in Bálint's syndrome, which is considered a hallmark of PCA since the disorder was first identified by Benson and colleagues (1988). As with neglect, simultanagnosia is a frequently reported as a symptom of PCA (Benson, Davis & Snyder, 1988; Tang-Wai et al., 2004; McMonagle, Deering, Berliner & Kertesz, 2006). Simultanagnosia is a rare deficit, which impairs an individual's ability to perceive more than one object simultaneously, and is generally conceptualised as a disorder of visual attention (Huberle & Karnath, 2006; Chechlacz et al., 2012).

There is some debate over the specific cognitive processes underpinning the presentation of simultanagnosia. There are two main neuro-cognitive mechanisms by which simultanagnosia has been proposed to be subsumed (Neitzel et al., 2017). The first of which, applying Bundesen's (1990) Theory of Visual Attention, postulates that the cause may be a slowing in the rate of visual information processing (Chechlacz et al., 2012; Neitzel et al., 2017). The second account suggests that simultanagnosia is the result of a reduced visual short-term memory storage capacity (Neitzel et al., 2017; Chechlacz et al., 2012). While the latter is conceptually neat, it appears rather a simplified view of what is a complex symptom; the behavioural consequence of simultanagnosia may appear to be a reduced visual STM capacity, but recent studies imply that earlier visual processing systems are implicated in the symptoms etiology. For example, some authors report that simultanagnosia is the consequence of a narrowed attentional window, thus leading the individual to be unable to perceive objects outside of this contracted field (Khan et al., 2016; Beh et al., 2014). Another conceptualisation, taking a more object-centered approach, is that it is the result of a deficit in global processing (Chechlacz et al., 2012). What is clear is that there is little agreement on the processes driving

simultanagnosia, and further investigation is necessary. Further discussion on theories and proposed cognitive processes, which may drive simultanagnosia, are discussed in greater detail in Chapter 5.

Deficits in object perception are reported as the third most common symptom of PCA by Crutch et al. (2017). Object perception requires both the ability to parse the object from the visual scene (through the process of figure-ground segmentation), as well as the capability to identify the object (via stored semantic object representations). Attributing a cause to observed deficits on object perception in patients with PCA is complex due to the converging influence of other symptoms on successful object perception. Both neglect and simultanagnosia, for example, will likely impact the patient's ability to identify an object correctly.

It should be noted, however, that the processes underpinning figure-ground segmentation and those leading to simultanagnosia may not be not the same. Figure-ground segmentation is the process by which the visual system organises a visual scene by parsing objects from their backgrounds (Kimchi & Peterson, 2008). There is evidence to suggest that figure-ground segmentation is a process that occurs outside of attention, and is generally conceptualised as a bottom-up process (Kimchi & Peterson, 2008).

In contrast, simultanagnosia is likely to be a disorder of visual attention whether this is due to a narrowed attentional window, slowed visual attentional processing, or indeed a global processing deficit. It has been observed that patients with simultanagnosia have relatively preserved single-object perception, and thus an advantage is observed for these patients when items are grouped into a single perceptual unit, rather than when multiple segments are presented in the visual fields (Mazza, 2017). According to the 'object-file' view on object perception, a series of temporary representations of real-world objects (object-files), distinct from representations stored in long-term recognition networks, are developed in a stage of object identification also

described as 'individuation' (Kahneman, Treisman & Gibbs, 1992; Mazza, 2017). A recent review of the evidence found that simultanagnosic patients may have intact object individuation, but demonstrate deficits in object identification, suggesting hierarchical processing in object perception (with object individuation preceding object identification), a view supported by recent neuroimaging research (Mazza, 2017). These results, among further evidence that multiple object processing may not be completely lost in simultanagnosia patients, are discussed in detail in Chapter 5.

Conceptually, therefore, it seems plausible that patients who experience simultanagnosia will have deficits in figure-ground segmentation due to associated deficits in object identification under ideal (non-overlapping) conditions. One manner of assessing figure-ground segmentation abilities is through the use of multiple overlapping stimuli, where the participant is required to identify the individual objects in the figure. In order to perceive overlapping objects the participant would need to successfully segregate and identify all objects in the scene - something simultanagnosic patients would, by definition, be unable to do (see Appendix 11).

The second element to object recognition, once the coherent whole form has been identified from its background through the process of figure-ground segmentation, is that of object recognition. Patients with PCA often report difficulty in locating or identifying objects (McMonagle, Deering, Berliner & Kertesz, 2006; Shakespeare, Ryan, Petrushkin & Crutch, 2012). Deficits in object recognition/identification are often reported as a detail in symptom profiles in studies of patients with PCA and are occasionally formally assessed, despite the inherent difficulties of testing such a function in patients whose visual processing is so compromised (McMonagle et al., 2006; Ardila, Rosselli, Arvizu & Kuljis, 1997; Caixeta et al., 2013). It seems likely that deficits in object identification in patients with PCA are driven by early visual processing deficits and symptoms such as neglect and simultanagnosia, rather than by a deficit in accessing stored semantic knowledge of the object. In other words, perhaps it is

not that these patients do not remember what a dog is, but rather that they can't see that it is a picture of a dog in the first place.

The next most prominent symptom of PCA is that of constructional dyspraxia (Cruch et al., 2017). Constructional dyspraxia, or visuo-constructional apraxia (VCA) is a term, which refers to impaired drawing or building performance (Berti, Garbarini & Neppi-Modona, 2015; McIntosh, Ambron & Della Sala, 2008). Deficits in constructional abilities are often an early sign of degenerative dementia (Kirk & Kertesz, 1991). Some have proposed that these degraded drawing abilities may be due to impaired spatial cognition, and therefore may be associated with a greater likelihood of associated environmental agnosia in an individual (Henderson, Mack & Williams, 1989; Monacelli, Cushman, Kavcic & Duffy, 2003). Notably, environmental agnosia is the next most common symptom following constructional dyspraxia observed in PCA according to the survey report by Crutch and colleagues (2017). An additional symptom which can be detected on tests of VCA is that of closing-in behaviour (CIB), which is the tendency for the copy of an image to be drawn inappropriately close to, or on top of, the copied image (McIntosh et al., 2008).

CIB is often observed in patients with severe VCA, however there is evidence that CIB may be an independent process to VCA (Conson, Salzano, Manzo, Grossi & Trojano, 2009). CIB is increasingly common with progressively more severe dementia, and has been estimated to be equally prevalent in AD and FTD (Ambron, McIntosh, Allaria & Della Sala, 2009). CIB has been hypothesized to be a 'compensatory' behavior, which aids in overcoming deficits in visuospatial and/or working memory. An alternative hypothesis has been posed, namely the 'attraction' hypothesis, which suggests that CIB may be the result of a primitive behaviour which likely requires fewer attentional resources and thus implies that CIB may be a clinical indicator of attentional deficits (McIntosh, Ambron & Della Sala, 2008). At the time of writing, no formal assessment of closing-in behaviour has been conducted in patients with PCA, therefore the inclusion of such a test is a novel contribution to the understanding of PCA symptomology.

4.0.3 Justification for Screening Test Assessments

The formal classification framework provided by Crutch et al. (2017) is the most detailed account available of the most common symptoms and the core cognitive features, which are indicative of PCA. The next progressive step from this classification framework would be a more clearly defined set of clinical cognitive criteria with associated recommendations for sensitive and specific diagnostic tests to be used in investigating the presence of these symptoms.

The screening battery herein consists of tests selected to probe these four most common symptoms, as described by Crutch et al. (2017); space perception deficits (considered to include neglect as well as early visual form processing for the purpose of this investigation), simultanagnosia, object perception deficits (including both figure-ground segmentation and object recognition), and constructional dyspraxia (VCA and CIB). In addition, the symptom of optic ataxia, which is the 8th most common cognitive feature in classification level 1 (see Figure 4.2) has been 'promoted' and included as a target symptom of interest given its prominence in Bálint's syndrome. Subsequent laboratory-based assessments (reported in Chapters 5 and 6) further magnify these target symptoms and address their characteristics in greater detail.

The assessments included in this battery were therefore selected in order to provide as detailed and as widespread an insight as possible into a range of early visual and visuomotor symptoms, which may be demonstrated in patients with PCA as well as patients with other NDDs. The assessments within this screening battery cover seven of the core cognitive features of PCA as detailed in the formal classification framework by Crutch and colleagues (2017). The core cognitive features assessed include: space perception deficits, simultanagnosia, object perception deficits, constructional dyspraxia, optic ataxia, alexia, and finger agnosia (Crutch et al., 2017). In addition, tests of

memory and executive functions were included in the battery – which are often relatively spared in PCA (Crutch et al., 2017).

For clarity of reporting, assessments within the present screening battery are henceforth organised under eight main domains. Details of the assessments included in each domain are presented in brief here (and in greater detail in Section 4.1.5) and justifications for the inclusion of each domain type are presented below.

4.0.3.1 Memory

Memory is perhaps the most over-represented symptom in any screen of dementia, but was included within this battery in order to provide a general insight into the memory abilities of the patients herein, and possibly to provide an indication of disease progression.

4.0.3.2 Elementary Visual Features

Early visual processing deficits were investigated within this screening battery using a number of assessments included in the Birmingham Object Recognition Battery (BORB) assessing elementary visual features of objects (Riddoch & Humphreys, 1993). Higher-order visual processing deficits are often cited more frequently in literature, presenting common symptoms associated with PCA, but many of these deficits are likely to be driven by deficits in more basic visual processing (Crutch et al., 2012). Therefore deficits in early visual processing were predicted to be observed in patients with PCA within this sample. Tests addressing some of these early visual processing abilities which relate to space processing of objects (including length, size, orientation and gap match tests) were thus included.

4.0.3.3 Perception of Multiple Figures

As discussed earlier in the introduction to this chapter, perception of multiple figures is impaired in patients who demonstrate symptoms of simultanagnosia. The test of perception of multiple figures which was included serves a dual function within this battery, as it is used to assess both simultanagnosia as well as figure-ground segmentation. As discussed previously, a patient with simultanagnosia will demonstrate deficits in perception of multiple figures regardless of whether they are presented overlapping or not overlapping, however, a patient who demonstrates no simultanagnosia but does demonstrate a deficit in figure-ground segmentation will show a deficit for overlapping figures only. These abilities were assessed by creating a composite 'Cost of Overlapping' and 'Cost of Pairs' score, further details of which are presented in Section 4.1.5.3 .

4.0.3.4 Object Perception

A cluster of object perception tasks was included within the screening test battery. Object perception or tests of visual recognition challenge the ventral stream of visual information processing, according to the dual stream hypothesis of visual processing (Goodale & Milner 1992; Milner & Goodale, 2008). Experiments which address the visual processing subserved by the dorsal "where" pathway, are reported in Chapter 7. Visual agnosia (and finger agnosia, discussed later) is a symptom which is cited frequently in case studies of patients with PCA (Benson, Davis & Snyder, 1988; Mizuno, Sartori, Liccione, Battelli & Campo, 1996; Berthier, Leiguarda, Sarkstein, Sevlever & Taratuto, 1991). Given the prominence of this symptom within the typical profile of PCA, it was of interest to assess these abilities as part of this battery.

4.0.3.5 Constructional Ability

A simple test of constructional ability – the Modified Luria Alternating Square and Triangles task (M-LAST) was included within this battery to provide an

overview of any presence of VCA or of CIB. This simple paper-and-pencil task has not previously, at the time of writing, been applied in the assessment of patients with PCA, therefore the inclusion of this task within this battery represents a novel application.

4.0.3.6 Spatial Attention

The core cognitive features of PCA identified by Crutch et al. (2017) names a 'space perception deficit' as one of a number of defining features of PCA. As discussed previously, this general term is not defined, but is taken to imply visual neglect (as well as elementary visual feature processing deficits) (Halligan, Fink, Marshall & Vallar, 2003). Visual neglect is an oft-cited symptom of PCA, therefore within this screening battery visual neglect is investigated using two well-established assessments: a cancellation and a line bisection task. Cancellation tasks are frequently cited as valuable tools in the assessment of visual neglect (Ferber & Karnath, 2001; Halligan, Cockburn & Wilson, 1991; Peru et al., 2017). The present battery includes both a visible (visual feedback provided) and an invisible (visual feedback withheld) condition. There is some evidence that invisible cancellation may reveal more neglect than visible cancellation tasks (Wojciulik, Rorden, Clarke, Husain & Driver, 2004). Similarly, line bisection tasks are commonly used to assess visual neglect (Ferber & Karnath, 2001; Halligan et al., 1991; Peru et al., 2017). In addition to the traditional condition of line bisection, a 'gap bisection' task condition is included within this battery – where respondents must touch the centre point between two dots (i.e. the midpoint of the 'gap'). The gap bisection subtest has not previously, at the time of writing, been applied to individuals with PCA, therefore inclusion of this subtest provides a novel opportunity to gain further insight into possible neglect-like behaviour within this population.

4.0.3.7 Executive Control of Attention

Given the likelihood that patients with PCA may demonstrate deficits in tasks assessing visual attention – it was of interest to assess whether other forms of

attention might additionally be impaired. As such, the Test of Everyday Attention was included within this test battery. Inclusion of this task allowed for an additional experimental hypothesis to be addressed, which is presented in Chapter 5.

4.0.3.8 Additional Tests

Three additional assessments were included within this battery. Brief tests of alexia and of finger agnosia were included as they are symptoms often cited with reference to PCA and feature as the 9th and 16th core clinical feature of PCA in the formal classification framework presented by Crutch and colleagues (2017), (Ardila, Rosselli, Arvizu & Kuljis, 1997; Crutch et al., 2017; Caizeta et al., 2013; Meek, Shelton & Marotta, 2013). The Test for the Reception of Grammar was also included within this battery as a simple language assessment. This test also has not, at the time of writing, been applied in the assessment of patients with PCA, therefore may present the opportunity for a further novel insight into the symptom profile of PCA patients.

4.0.4 Aims

The aims of this screening phase of assessment were threefold. The primary aim was to establish the diagnostic utility of certain assessments at discriminating patients with PCA from patients with a diagnosis of a different neurodegenerative disease (NDD). The secondary aim was to investigate the frequency of primary visual symptoms in patients with other NDDs, as this has not been formally investigated prior to this study. The third aim was to identify patients who demonstrate visual or visuomotor impairment, which may then be a useful predictor of performance in subsequent, more detailed lab-based assessments, which these patients would be invited to participate in.

4.1 Method

4.1.1 Ethical Approval

This study was reviewed by the South East Scotland Research Ethics Committee 02 and a favourable opinion was granted on the 13th May, 2015 (REC reference number: 15/SS/0068). National Health Service Management Approval was also sought and granted (R&D reference number: 2015/0246) on the 5th June 2015.

4.1.2 Recruitment

Clinical participants were recruited from The Anne Rowling Regenerative Neurology Clinic (ARC) at the Edinburgh Royal Infirmary, Scotland. Elaborative details on recruitment methodology are provided in the study protocol (Version 1.7) (Appendix 4).

Patients were identified as eligible for the study by their treating clinician or by the ARC on-site research support staff. Patients were approached who had previously consented to being contacted about research, and were therefore part of the Diagnosis Audit Research and Treatment (DART) Register. Recruitment took place for a period of 22 weeks from January to May 2016.

Table 4.1 below illustrates the inclusion and exclusion criteria for the study.

Inclusion Criteria	Exclusion Criteria
• Diagnosis of PCA, CBD, PPA, AD or FTD • Age over 18 years • Anticipated survival of more than 12 months	• Inability to understand the consent process • Enrolment in any other ongoing research project • Participants with severe diabetes, epilepsy, alcohol/substance-related disorders, severe head injury (that required intensive care setting hospitalization), traumatic brain injury (inclusive of subarachnoid haemorrhage) and any other significant medical illness (such as stroke) • Non-English speakers

Table 4.1: Inclusion and Exclusion Criteria for Clinical Recruitment

Those patients identified as eligible were sent a recruitment pack containing a participant information letter, a participant information sheet detailing what would be involved in the study, a notification of interest (NOI) form and a stamped addressed envelope in which to return the NOI form to the primary investigator (PI) (see Appendix 5 – 10 for copies of the forms).
After consultation at a dedicated PCA patient and carers meeting at the ARC on the 3rd March, 2015, it was clear that due to the difficulty many patients (particularly those with PCA) have with reading, provision of the study information in an alternative form was important. Therefore each letter and information sheet that patients received was made available in audiovisual format (Ingle, 2015).

The study was divided into two 'phases'. Patients were invited to participate in Phase 1 initially - the screening phase (reported in the present chapter). Once patients had completed the Phase 1 assessment, they were sent a new patient information letter, patient information sheet, and NOI form with envelope in order to indicate their interest in participating in Phase 2 of the study (the lab-based assessments, detailed in Chapters 5 and 6). Consent to participate in Phase 2 was taken separately from Phase 1. Patients indicated on their Phase 1 consent form if they were interested in receiving information about Phase 2. Further details on Phase 2 recruitment are presented in Chapter 5.

4.1.3 Participants

A total of 87 patients were identified as eligible for the study, and were sent a recruitment pack by the ARCs research support staff from January 10th to May 31st 2016. The flow diagram (Figure 4.3) below details the recruitment into this phase.

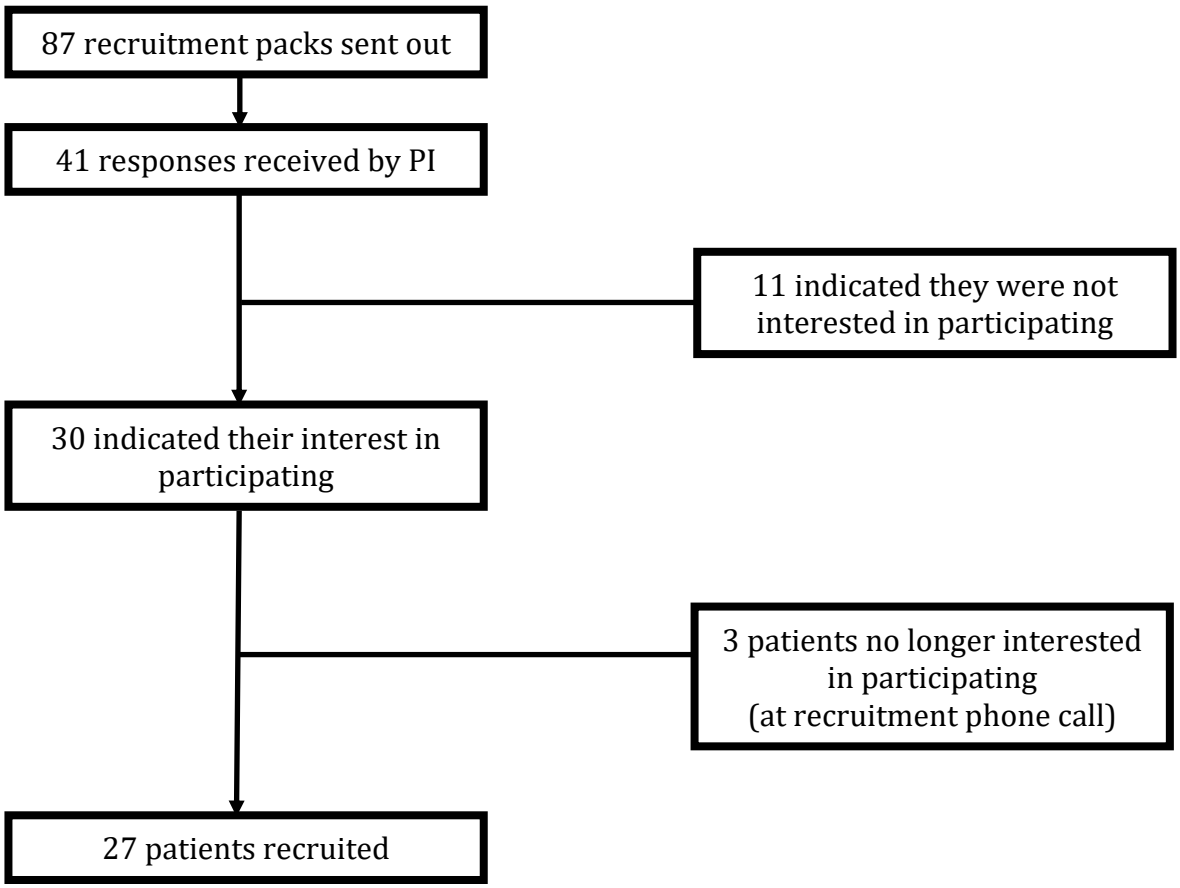


Figure 4.3: Recruitment into Phase 1 Flow Diagram

In total, 27 patients were recruited into Phase 1. For the majority of patients, the Phase 1 assessment was split across two appointments (further details in the procedure section below). After the first session one patient dropped out due to a bereavement, and follow-up on a second patient was not possible due to repeated missed appointments.

Diagnosis at the ARC is clinical: based on evidence from the patient's history (including information from relatives or caregivers), examination, and additional investigations such as neuroimaging or cerebrospinal fluid (T. Bak, personal communication, 12th June 2017).

Table 4.2 below provides demographic characteristics of the different diagnostic groups to which the 27 patients belonged.

Diagnostic Group No.	Diagnostic Group Description	Number of Patients in Group	Median Age at Date of Consent [range]	Gender		Mean months since diagnosis [range]
				Female	Male	
1	PCA	6	62.13 [51.34-69.59]	4	2	27 [8-40]
2	AD	8	65.98 [55.72-71.38]	4	4	19.50 [4-41]
3	FTD	8	66.52 [57.84-73.52]	3	5	28.63 [8-41]
4	Aphasia	3	70.36 [64.48-71.51]	2	1	32.67 [12-46]
5	LBD/CBD	2	70.42 [62.79-78.05]	1	1	33.50 [8-59]

Table 4.2: Demographic Characteristics of Patients in Phase 1
Note: mean months since diagnosis refers to the time between initial diagnosis to screening testing in the present investigation.

4.1.4 Procedure

The Phase 1 battery took around 90 to 120 minutes to complete. Patients were advised that the testing session could be split across two separate appointments, and 62.9% (n=17) patients chose to do this. This minimized fatigue and ensured that the patient's welfare was prioritized. After each subtest patients were asked if they wanted to take a break, and the PI checked whether patients were happy to continue with the session.

During the initial phone call to book an appointment patients were advised that they could choose where they would like to meet for their test appointment. The majority of patients (96.3%, n=26) chose to be tested in their own homes, and 1 patient (3.7%) chose to be tested in a private assessment room within the University of Edinburgh's Department of Psychology.

At the start of the appointment patients were invited to ask any further questions before completing a consent form (Appendix 10) (completed by proxy when necessary). Presentation order of the subtests was consistent across patients (Table 4.3 in Section 4.1.5 below presents the tests and running order).

4.1.5 Materials & Measures

The screening battery for Phase 1 was chosen to include a range of assessments which would be sensitive to deficits associated with damage to higher order visual brain areas, therefore highlighting any specific visual recognition, visual attention, and visuomotor deficits which patients may exhibit.

Table 4.3 below details the assessments included in Phase 1. These tests were selected in order to target specific cognitive processing abilities and are grouped and subsequently analysed within these categories for clarity of interpretation.

Assessment Category	Test	Subtest	Full or Abridged* Version	Running Order
1. Memory	Rivermead Behavioural Memory Test – 3rd Edition			
		Story Recall - Immediate	Full	1
		Story Recall - Delayed	Full	12
(preliminary screen)	Birmingham Object Recognition Battery			
		1: Copying of elementary shapes	Abridged	2
2. Elementary visual features		2: Length match test	Abridged	3
		3: Size match test	Abridged	4
		4: Orientation match test	Abridged	5
		5: Position of gap match test	Abridged	6
3. Perception of multiple figures		6: Overlapping figures	Abridged	7
4. Object Perception		7: Minimal feature match	Abridged	8
		10A: Object decision (hard)	Abridged	9
		10B: Object decision (easy)	Abridged	10
		13: Picture naming (short version)	Abridged	11
5. Constructional ability	Modified Luria Alternating Square and Triangles		N/A	14
6. Spatial attention	Cancellation Test			
		Visible Condition	N/A	16
		Invisible Condition	N/A	17
	Line Bisection Test			
		Line Condition	N/A	18
		Gap Condition	N/A	19
7. Executive control of attention	Test of Everyday Attention			
		Elevator Counting	Full	21
		Elevator Counting with Reversal	Full	22
		Elevator Counting with Distraction	Full	23
8. Additional tests	Alexia Passage		N/A	13
	Finger Agnosia		N/A	15
	Test for the Reception of Grammar		Full	20

Table 4.3: Assessments included in the Phase 1 Screening Battery
* Where abridged version is used, 1 page of stimuli were used from each subtest, unless otherwise specified in the method section below.
Where N/A is noted, this indicates that the test used was a custom-designed assessment, which was delivered in full, but has no established mode of use.

Materials required for the assessment battery were the following;

- Rivermead Behavioural Memory Test reporting form

- Stimuli sheets for each subtest (these were spiral bound into an assessment book): this included all the BORB subtests (in A4 format) (see Appendix 11 for BORB test materials)
- Spiral bound Test for the Reception of Grammar stimuli sheets (A4 format) (see Appendix 12 for example stimulus page)
- An HP Envy Rove Touchscreen Computer (active display area 423.33 x 238.13mm, resolution 1600 x 900 pixels) for presentation of the Cancellation Test, the Line Bisection Test, and for presentation of the Test of Everyday Attention audio files.
- HP Wireless Keyboard (model number: KBRF7171)
- HP Wireless Mouse (model number: MORFGIUO)
- Stopwatch
- A4 sheets with the BORB test 1, Alexia Passage, and Modified Luria Alternating Square and Triangles forms.
- Olympus VN-7800PC Digital Voice Recorder for Alexia recordings
- Aphasia reporting cards

Aphasia reporting cards were created in anticipation of deficits, which some patients may have in responding verbally to the PI during the assessments. Patients with language or speech deficits were given instructions on how to respond using these cards before the assessments commenced. Figure 4.4 below shows these cards.

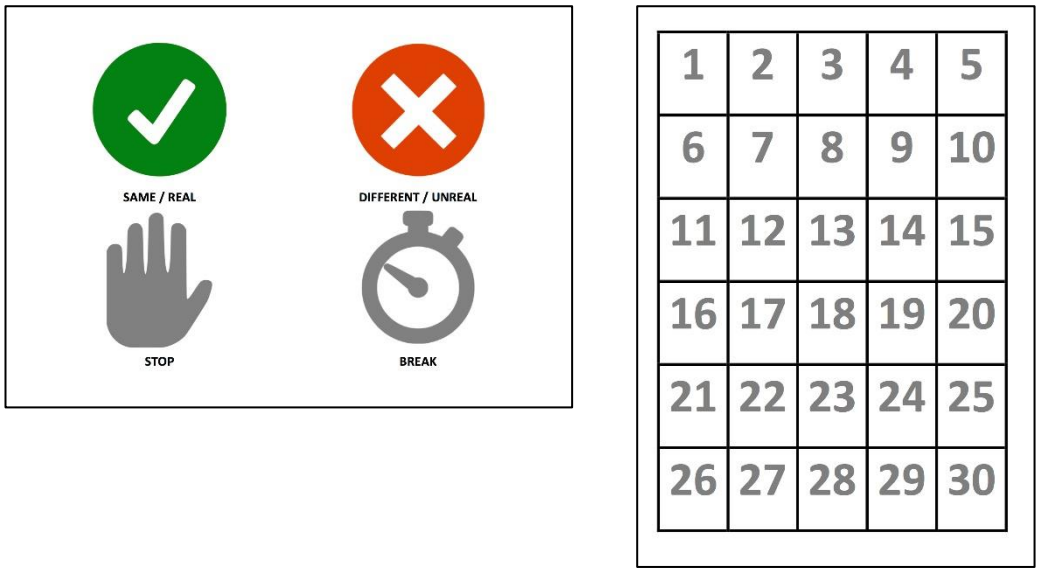


Figure 4.4: Aphasia Reporting Cards

In addition, data from patients' most recent ACE-III (Hsieh, Shubert, Hoon, Mioshi & Hodges, 2013) examinations were obtained from the Edinburgh Cognitive Diagnosis, Audit, Research and Treatment register (DART). The ACE-III tasks are divided into five different domains: attention, memory, fluency, language and visuospatial (Hsieh et al.). The ACE-III is scored out of a maximum of 100, with a greater score indicating better cognitive function (Hsieh et al.). The most recent ACE-III scores from each patient were analysed in order to give a broad description of the state of dementia for each group. Table 4.4 below provides an overview of these data.

Diagnostic Group	Patient No.	ACE-III Total Score [max 100]	Time before/after screening assessment (months)
1	1	61	5
1	2	65	22
1	3	34	* 7
1	4	43	21
1	5	71	4
1	6	71	0
2	14	51	21
2	17	78	17
2	18	76	13
2	19	62	20
2	20	ND	15
2	21	74	8
2	22	52	4
2	24	75	4
3	7	29	1
3	9	75	16
3	10	ND	32
3	11	88	17
3	13	76	10
3	15	97	30
3	23	82	7
3	25	73	12
4	8	95	12
4	16	40	12
4	27	93	6
5	12	33	23
5	26	82	1

Table 4.4: ACE-III Total Score and Testing Information
Note: Patient data for diagnostic group 4 and 5 are provided but are greyed out as patients were excluded from further analysis.
* Indicates that ACE-III testing occurred the specified duration *after* screening testing. All other ACE-III results were recorded prior to screening testing.
Key: ND = no data available on ACE-III test scores
Diagnostic Group Key: 1 = PCA, 2 = AD, 3 = FTD, 4 = Aphasia, 5 = LBD/CBD

4.1.5.1 Memory

The RBMT-3 story recall (immediate and delayed condition) subtest was included in the battery in order to provide a measure of memory. Patients completed Version 1 of the test (Wilson et al., 2007).

The ratio between the immediate recall and delayed recall score was intended to be the dependent variable of interest, however in practice on this test the

immediate recall score was <10% for 60% (n = 15) of participants: indicating a floor effect. Therefore only immediate recall was analysed further on this test.

The RBMT-3: Story Recall subtest was scored according to the RBMT manual: where points are allocated to each semantically similar or correctly recalled item (Wilson et al., 2007). The RBMT-3 normative data are based on a sample of 333 individuals (172 female, 161 male), although no information is available on how many were included in the 65-74 age band (Wilson et al., 2007). Raw scores were converted into scaled scores according to the manual (Wilson et al., 2007).

4.1.5.2 BORB: Subtest 1

BORB Subtest 1- copying of elementary shapes – was included in an abridged, five-stimulus form as a 'fork in the road' test: a way to inform whether version A or version B (intended for patients with unilateral neglect) of the subsequent BORB subtests should be presented. Version B of the aforementioned subtests presented pairs of stimuli vertically rather than horizontally in order to minimize any effects of impaired processing for one side of space, which would be anticipated in patients who demonstrate symptoms of neglect (Riddoch & Humphreys, 1993). If qualitative assessment of patients' drawings indicated neglect, for example details were consistently omitted from one side of the drawing or a marked inattention to one area of space on the page was observed, then version B of the BORB subtests were presented which follows the guidelines published by Riddoch & Humphreys (1993). The results of this test are therefore not formally analysed, but are presented in Chapter 7.

4.1.5.3 Elementary Visual Features

BORB subtests 2-5 had two alternate versions (see Section 4.1.5.2 above for details). The tests involved the matching of: (2) line length, (3) stimulus size, (4) line orientation, and (5) position of a gap on two circles (Riddoch & Humphreys,

1993). Participants were required to state whether pairs of stimuli were the same in these key characteristics, or different. For example, "are these two lines the same length, or different lengths?" These subtests were included as a way to gain general insight into the early visual processing abilities of the patients.

Patients were shown each stimuli pair one at a time by using a card 'window'. This allowed for the patients to consider only one set of stimuli at a time and aimed to minimize the effects of simultanagnosia or visual crowding from additional stimuli on responses.

Control means and standard deviations (SD) were taken from the BORB (Riddoch & Humphreys, 1993), and were adjusted for the purposes of cut-off calculations to create a proportional mean/SD relative to the number of stimuli in the full test versus the number of stimuli presented to patients in the attenuated test.

4.1.5.4 Perception of Multiple Figures

BORB Subtest 6, the overlapping figures test, requires segmentation of objects from their background (Riddoch & Humphreys, 1993). This test serves a dual function within this battery as it may be used to assess both simultanagnosia as well as figure-ground segmentation.

Patients were presented with an abridged version of two of the three stimuli categories; namely letters and line drawings. The geometric shapes category of stimuli was omitted as during piloting of the test battery it was found that two of the shapes could be identified by the same moniker (specifically, the + and x shapes could both be identified as 'cross'). Patients were therefore presented with 1 page of stimuli from each condition for the letters (single stimuli, paired non-overlapping, paired overlapping, triplets non-overlapping and triplets overlapping) and line drawing (single stimuli, paired non-overlapping, and paired overlapping) categories (see Appendix 11 for stimuli sheets).

In order to analyse these data composite mean times for each patient on single non-overlapping stimuli, paired non-overlapping and paired-overlapping were generated. The composite single stimuli mean time was taken as the individual's baseline time. From this a 'cost of pairs' (CoP) ratio score was then calculated between single non-overlapping and paired non-overlapping stimuli, and a 'cost of overlapping' (CoO) ratio score was calculated between paired non-overlapping and paired overlapping stimuli (see formulae below for details). No further analysis was possible on the triplets non-overlapping and triplets overlapping as this condition is not available for the line drawing subtest. This allowed for insight into whether symptoms of simultanagnosia or figure-ground segmentation issues were present.

$$CoP = \frac{composite\ paired\ non\text{–}\ overlapping\ stimuli\ mean}{composite\ single\ stimuli\ mean}$$

$$CoO = \frac{composite\ paired\ overlapping\ stimuli\ mean}{composite\ paired\ non\text{–}\ overlapping\ stimuli\ mean}$$

Patients with simultanagnosia would be predicted to have a high CoP score and very little to no difference between the CoP score and the CoO score. Conversely, patients with no simultanagnosia but with figure-ground segmentation problems would have a very low CoP score but a high CoO score.

4.1.5.5 Object Perception

BORB Subtest 7 – minimal feature match – requires patients to choose which of two objects is the same as the target object, but seen from a different viewpoint. This test therefore requires mental spatial rotation of the target object, as well as intact semantic knowledge.

The object decision BORB Subtests 10A (hard) and 10B (easy) were presented as a test of both access to stored knowledge and simultanagnosia. Patients were

presented with single line drawings and instructed to respond as to whether the item presented was real or unreal.

The short picture-naming subtest, BORB Subtest 13, was a simple test in which patients were shown different line drawings and asked to name the item. This test highlights any issues with naming, language function, and to some extent vision (Riddoch & Humphreys, 1993).

4.1.5.6 Constructional Ability

The Modified Luria Alternating Square and Triangles (M-LAST) test was a simple copying test, used to identify symptoms of visuo-constructional apraxia (VCA) as well as closing-in behaviour (CIB) (Chin et al., 2005; McIntosh, Ambron & Della Sala, 2008). Patients were required to copy three simple geometric stimuli, presented in Figure 4.5 below. These stimuli were presented on an A4 page with equal space under each one, which was the intended space for copies to be drawn.

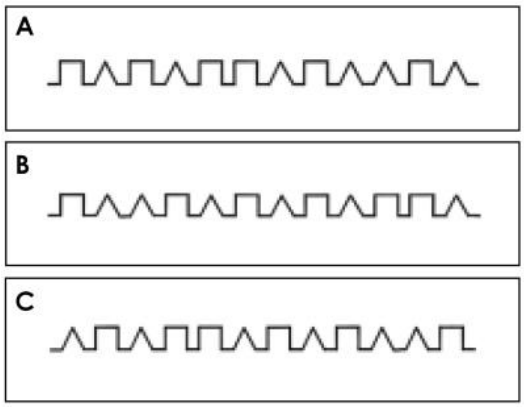


Figure 4.5: Stimuli Used in the M-LAST test.

Patient responses were then coded to determine levels of VCA and CIB using the qualitative assessment scale presented in Table 4.5 below.

Coding System for M-LAST Test			
Visual Constructional Apraxia (VCA)			
0	**1**	**2**	**3**
Good copy	Recognisable but mildly impaired	Very impaired, barely recognisable	Not recognisable
Closing-in Behaviour (CIB)			
0	**1**	**2**	**3**
None evident	Inclined drawing, not touching the stimulus box	Drawing touching the stimulus box	Drawing touching the figure within the stimulus box

Table 4.5: Coding System for M-LAST Test

4.1.5.7 Spatial Attention

The line bisection and cancellation tasks were included as well-established and frequently utilised tests of neglect (Jewell & McCourt, 2000; Reuter-Lorenz & Posner, 1990; Ferber & Karnath, 2001; Keller, Schindler, Kerkhoff, von Rosen & Golz, 2005). The methodology and elaborative results for the cancellation and line bisection assessments are reported and discussed in Chapter 5. For simplicity of presentation, however, initial analysis is reported within this chapter.

4.1.5.8 Executive Control of Attention

The TEA elevator counting subtests included in this battery measure selective attention, sustained attention and attentional switching (Robertson, Ward, Ridgeway & Nimmo-Smith, 1994; 2009). Version 1 of each was used. No prior literature could be found at the time of writing that demonstrates the use of the TEA Elevator Counting Subtests in patients with PCA, therefore this is a novel use of a well-established test of sustained attention within a population who are likely to demonstrate deficits on attentional tasks.

The TEA subtests were scored according to the TEA manual. Raw scores were transformed into scaled scores, using the method presented in the TEA manual

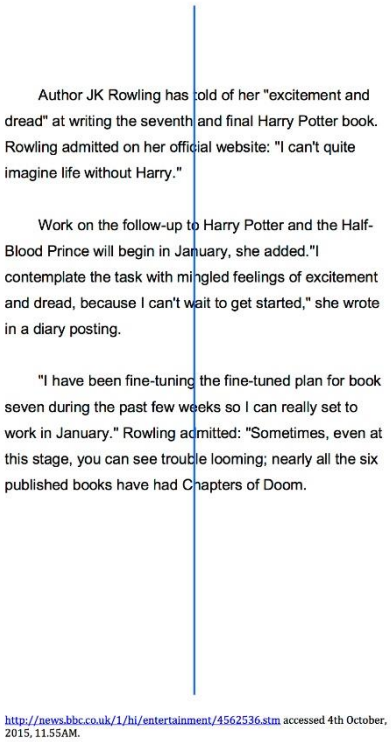
(Robertson, Ward, Ridgeway & Nimmo-Smith, 1994). The TEA normative data for the age group 65-80 are based on a sample of 43 individuals (no information was available on gender) (Robertson et al., 1994). The scaled scores are based on a mean of 10 with a standard deviation of 3, and a range of 1-19 (Robertson et al., 1994). No scaled or percentile scores are provided for the first subtest, 'elevator counting', because of the ceiling effect in control subjects. The manual instead suggests that greater than one error on this subtest could be considered abnormal. Therefore for analysis of this condition the raw scores were used.

Scaled scores and equivalent percentile ranges for each patient/participant were then identified using the manual (Robertson, Ward, Ridgeway & Nimmo-Smith, 1994). These results are qualitatively reported in the results section of this chapter.

4.1.5.9 Additional Tests

Patients were asked to read out loud a short passage (Appendix 13), while being recorded on a Dictaphone, in order to screen for symptoms of alexia. The passage was selected and presented using an adapted version of the method presented by Yong, Rajdev, Shakespeare, Leff & Crutch (2015).

In order to qualitatively assess for symptoms of alexia the recordings for each patient were analysed and coded. Errors were coded as any word that was misread/mispronounced, omitted completely, or inserted. In addition, in order to screen for reading neglect the passage was split with a virtual dividing line down the centre of the passage (See Figure 4.6 below). Following this, words that occurred on the left hand side were classified as left-sided words, and words that occurred on the right hand side were classified as right-sided words. This allowed for words to be coded as errors or hits on either side of the page, which allowed for insights into whether lateralised errors in reading were occurring.



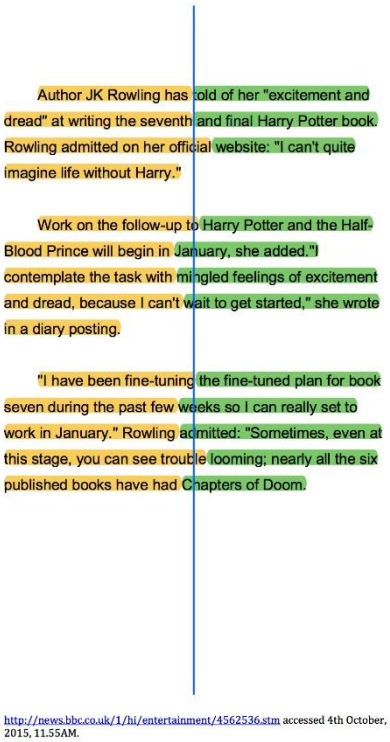
Author JK Rowling has told of her "excitement and dread" at writing the seventh and final Harry Potter book. Rowling admitted on her official website: "I can't quite imagine life without Harry."

Work on the follow-up to Harry Potter and the Half-Blood Prince will begin in January, she added."I contemplate the task with mingled feelings of excitement and dread, because I can't wait to get started," she wrote in a diary posting.

"I have been fine-tuning the fine-tuned plan for book seven during the past few weeks so I can really set to work in January." Rowling admitted: "Sometimes, even at this stage, you can see trouble looming; nearly all the six published books have had Chapters of Doom.

http://news.bbc.co.uk/1/hi/entertainment/4562536.stm accessed 4th October, 2015, 11.55AM.

A virtual central dividing line was placed on the page.



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http://news.bbc.co.uk/1/hi/entertainment/4562536.stm accessed 4th October, 2015, 11.55AM.

Words occurring on the left of this virtual line were coded as left sided words, and words occurring on the right side were right-sided words.

Figure 4.6: Alexia Passage Lateralised Error Coding System

Words that were bisected by the dividing line were coded as belonging to the side on which the majority of the letters of that word occurred.

Finger agnosia is one of the four major symptoms associated with Gerstmann's Syndrome (Ardila, 2014) and was therefore included, in brief, in the battery. Patients were asked to name fingers presented on the PI's left hand in a pseudorandom order. The PI held up their left hand, dorsal side towards the patient, and indicated the finger to be named by pointing with the index finger of the right hand. The assessment for finger agnosia used in this battery was a simplified version of one classically described by Gerstmann (1940). Table 4.6 below presents a list of allowable alternative names for each finger. Participants who failed to identify the finger with any one of the allowable identifiers had their response coded as an error

Finger Location	Allowable Identifiers
	Thumb
	Index finger Pointer / Pointing finger First finger Forefinger
	Middle finger Second finger
	Ring finger Third finger
	Little finger Pinkie finger Baby finger

Table 4.6: Finger Agnosia Allowable Finger Identifiers

Recognition of the middle three fingers is particularly vulnerable in finger agnosia, therefore most patients will likely identify the thumb and little fingers correctly (Rosca, 2007). Raw scores (out of a maximum of 5) were compared to a group of age- and sex-matched controls (see Chapter 5, Section 5.1.3.2 for details on this sample) from which cut-off scores for normality were generated. This assessment was brief and by no means could it be considered rigorous. It was included to give a general overview of whether symptoms similar to finger agnosia were detected.

The TROG-1 was used to assess language comprehension, and is advantageous to use in a population with suspected attentional and short-term memory impairments, as the sentence length is kept constant across tasks of different

syntactic complexity (Bak, Donovan, Xuereb, Boniface & Hodges, 2001; Bishop, 1989). This test has not been used to assess patients with PCA prior to this study, and therefore may provide a novel insight into language processing abilities within this population. A rule was applied in the administration of the TROG, whereby 2 or more errors in 3 consecutive blocks would result in the discontinuation of the test. This prevented both anxiety for the patients and time being wasted in delivering increasingly more complex blocks to patients who were unlikely to successfully comprehend them.

Analysis of the TROG was conducted by analysing the dependent variables of number of items correct (out of a maximum of 80), and number of blocks passed (out of a maximum of 20). Control normative data were extracted from Croot, Hodges & Patterson (1998).

4.2 Analysis

4.2.1 Analysis Methodology and Justification

Non-parametric statistical tests were used as standard for these data as assumptions of parametric testing, such as a normal distribution and equality of variances, were violated in the majority of cases. Consistently using non-parametric tests was additionally intended to aid consistency of presentation. Statistical testing was conducted using percentage scores, or mean percentage scores for domains in which a number of individual tests were combined.

This approach was used as there is evidence to suggest that using *z*-scores for small patient samples, particularly on tests where controls have a ceiling effect of performance, inflates the Type I error rate by exaggerating deficits (Crawford & Garthwaite, 2005; Crawford, Garthwaite, Azzalini, Howell & Laws, 2006). Crawford's *t*-score method is helpful and demonstrably more robust to the effects of skewness when compared to *z*-scores, but may only be used in single-case comparisons (Crawford & Garthwaite, 2005; Crawford, Garthwaite,

Azzalini, Howell & Laws, 2006). Therefore raw scores were converted into percentages (unless otherwise specified) as this allowed for each subtest within a domain to have an equal weighting on the domain total percentage score – calculated by creating a mean of the individual's percentage scores for each subtest within that domain. Given the complexity of this dataset and the relatively small participant numbers, using percentage total scores was considered the optimum way to create a shared scale of comparison of performance between the domains.

To classify patient performance as normal or abnormal, cut-off scores for normality were generated for each test for which control performance was not normally distributed. These scores were generated using Crawford's *t*-score formula, which reads as follows;

$$t = \frac{patient\ score - control\ mean}{control\ SD\sqrt{\frac{n+1}{n}}}$$

The critical values of *t* for each subtest were calculated using an online Student *t*-value calculator (Sloper, 2006). Scores were calculated using Microsoft Excel, and were checked using a published *t*-score calculator (Crawford & Garthwaite, 2002).

Following this, Crawford's formula was modified in order to generate the value of *c* (the cut-off) below which performance would be coded as abnormal;

$$\text{A)}\quad x = t \times \left(\left(control\ SD\sqrt{\frac{n+1}{n}}\right) + control\ mean\right)$$

$$\text{B)}\quad c = control\ mean - x$$

Exceptions were the RBMT-3 and TEA for which scaled scores were generated according to the respective test manual instructions (Wilson et al., 2007; Robertson, Ward, Ridgeway & Nimmo-Smith, 1994). For these subtests the cut-off for normal performance was calculated as -1.65 SDs from the control mean (Asch, 2005). In addition, BORB Subtest 6 – Perception of Multiple Figures – was analysed differently. The cut-off for normal performance was taken as the time to read one page of stimuli for the worst control, as reported in the manual (Riddoch & Humphreys, 1993). Control data for BORB Subtest 6 were very limited. The manual provides only the mean reading time per sheet for eight control subjects as well as the worst control score in seconds per sheet. Therefore, without any further information on standard deviations, calculating cut-offs for normal performance using a modified version of Crawford's formula was not possible. For this reason using the worst control time per sheet was considered the best way to determine a cut-off for normal performance.

Diagnostic group 4 (aphasia) and diagnostic group 5 (LBD/CBD) had only three and two patients respectively. Given that these numbers are too few to make meaningful quantitative group comparisons, and considering the striking diversity of disease progression between patients within these groups, these groups were removed from further analysis. However, for completeness, results from Group 4 and Group 5 on all assessment categories reported below are presented in Appendix 14.

The initial aim of this investigation was to establish the diagnostic utility of the tests within the screening battery for identifying patients with PCA when compared with patients with other NDDs. Therefore the AD and FTD groups were combined to create a composite 'other NDD' group which is subsequently used as a comparator for all further analysis. Plots with the fine-level detail of the AD and FTD group performances as well as the performance on individual subtests of a given domain are presented for reference, but analysis for a given domain was conducted on domain-total *t*-scores.

Data were first analysed at the group level in order to identify which abilities best distinguish samples of patients with PCA from those with other NDDs. Following this, sensitivity, specificity and diagnostic accuracy of each subtest was calculated in order to identify which tests are best able to detect PCA-specific behavioural responses and therefore may be the most accurate to use in a clinical setting.

4.2.2 Sensitivity Analysis

The general objectives of the present study are to find patterns of behaviour which distinguish patients with PCA from those with other NDDs. In order to achieve this, particularly in a limited sample of patients, the risk of misidentifying patterns as positive (type I errors) must be balanced against the possibility of missing patterns which are there (type II errors). At this early, exploratory stage of research it is important that possible 'clues' are not missed. Therefore, a balance between the probability rates of the two errors types must be struck. Further details are presented below which state the rates of type I and type II error probabilities accepted in the analysis of the screening assessments within this battery, and the justification for each.

Due to the low power associated with a small sample size such as the present sample, as well as the heterogeneity of these patients, there is a risk of increased type II error rates when using the conventional alpha criterion of 0.05. Figure 4.7 below demonstrates the effect size that would be required in order for a two-tailed test to reach an acceptable level of statistical significance with the standard alpha criterion of 0.05 and an equivalent power of 0.95 (the rate of type I and type II errors therefore being made equal). The resulting Cohen's *d* effect size of 1.81 falls between the magnitude descriptors of "very large" (1.20) and "huge" (2.0) (Cohen, 1988; Sawilowsky, 2009).

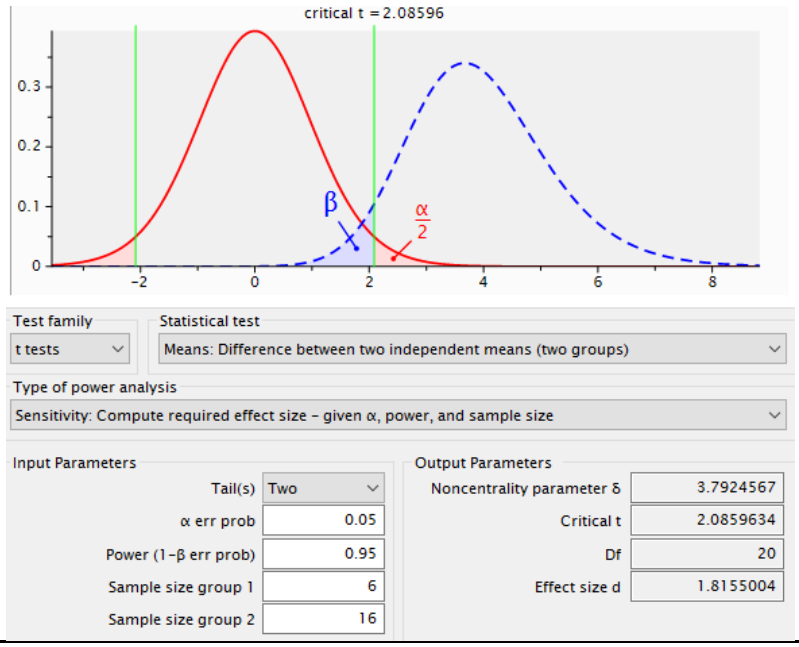


Figure 4.7: Sensitivity Analysis Using Standard Alpha Criterion of 0.05 and Power of 0.95

Clearly therefore, using an alpha criterion of 0.05 may be considered very conservative for the present sample. The requirement of such a large effect size to reach statistical significance is likely to result in the masking of clinically relevant differences between the groups in the present study.

Figure 4.8 below presents a plot contrasting the standard alpha criterion of 0.05 with an alternative alpha criterion of 0.1.

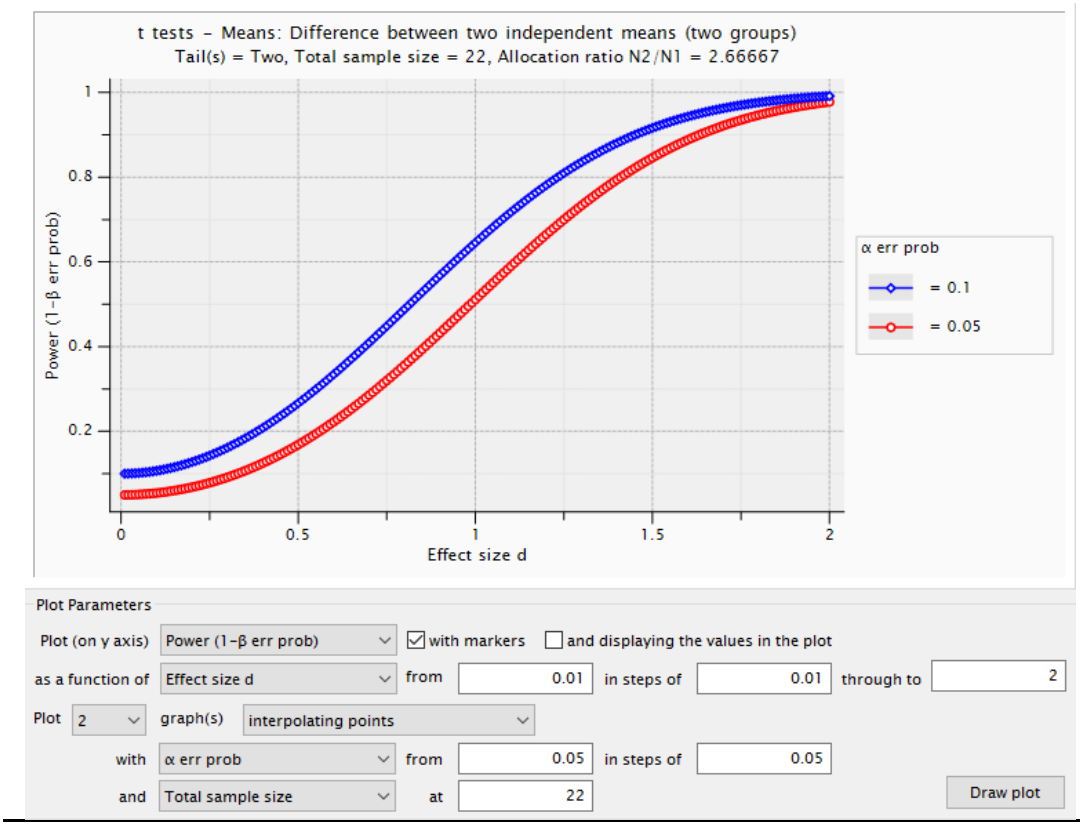


Figure 4.8: Sensitivity Analysis Contrasting an Alpha Criterion of 0.1 and 0.05

Using an alpha criterion of 0.1 would result in a power of 0.65 to detect a Cohen's *d* effect size of 1, which falls between the magnitude descriptors of "large" and "very large" (Cohen, 1988; Sawilowsky, 2009). Therefore with an alpha criterion of this value the risk of type I errors would be 10%, and type II would be 35%. Any results reaching statistical significance using this alpha criterion would demonstrate robust effect sizes according to standard definitions, indicating strong differences between the two groups. Consequently results that have a *p* value of up to 0.1 will be discussed as meaningful for the analyses conducted within this chapter. For clarity of reporting, all *p* values will be reported as exact values rather than the conventional range, and presented to three decimal places.

4.3 Results

4.3.1 ACE-III

Domain total subscores are heterogeneous for the ACE-III, therefore percentage scores were calculated in order to aid meaningful comparisons across domains.

The mean time between ACE-III testing and screening testing for the present study was 12.07 months (SD = 9.44).

Figure 4.9 below presents descriptive boxplots illustrating the distribution of ACE-III total scores (as percentage correct) for each diagnostic group. These data illustrate considerable variability both within- and between-groups.

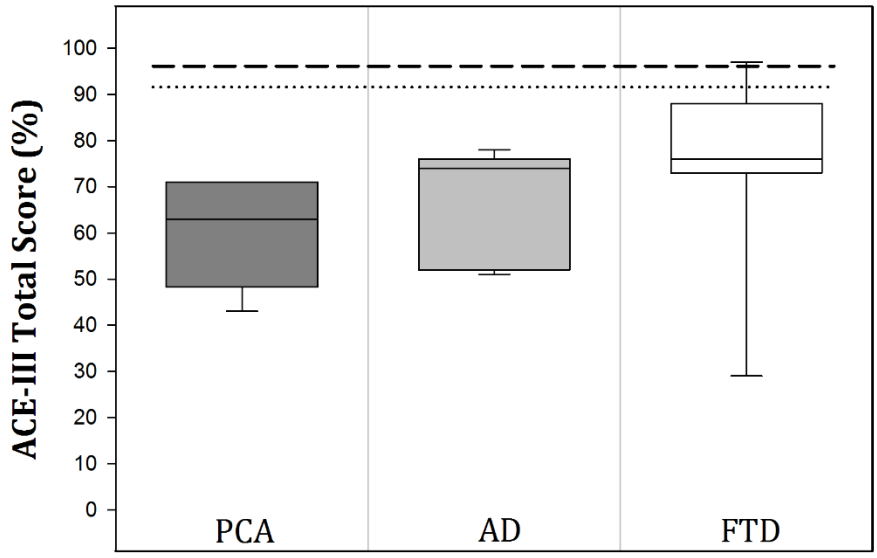


Figure 4.9: Boxplots Illustrating ACE-III Total Scores (percentage correct)
Key: — — — represents control mean, · · · · · represents lower cut off for normal performance

In order to gain further insight into these data, Figure 4.10 below presents a more detailed and elaborative insight into patient performance on the ACE-III.

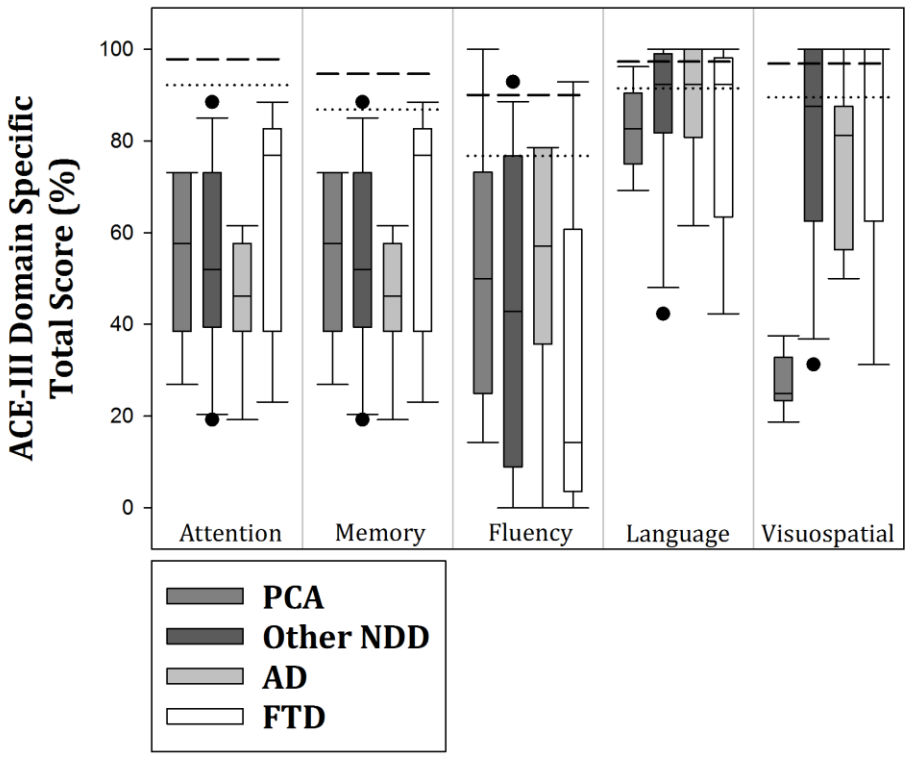


Figure 4.10: Boxplots Illustrating Percentage Correct Scores for Each Domain on the ACE-III
Note: Outliers are represented as black circles.
Key: — — — represents control mean, · · · · · represents lowest cut off for normal performance

	PCA			Other NDD			AD			FTD		
	N	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**
Attention	0	6	-	3	10	4	0	7	1	3	3	3
Memory	0	6	-	1	11	4	0	7	1	1	4	3
Fluency	1	5	-	3	9	4	2	5	1	1	4	3
Language	1	5	-	7	5	4	4	3	1	3	2	3
Visuospatial	0	6	-	5	7	4	1	6	1	4	1	3

Table 4.7: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on Each ACE-III Domain
Note: N = 'normal', greater than the level of lowest cut-off for healthy control performance. A = 'abnormal', below the level of lowest cut-off for healthy control performance, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest or for whom no data were available.
Note: Results from AD and FTD groups are presented for completeness, but are greyed out to indicate that these individual groups were not compared in further analysis.

Table 4.7 provides a summary of patient performance when compared to the cut-off score for normality. It is evident that patients with PCA appear to perform significantly worse on the visuospatial domain, with little variation in

performance, relative to their scores on all other domains on the ACE-III. This is a predictable finding, given the visuospatial deficits characteristic of PCA. Similarly, patients with other NDDs appear to perform worse on the fluency domain in relation to memory performance. This is a result of the relatively poor performance of patients with FTD (a finding additionally predicted within the literature on FTD specifically), particularly given the reliance on executive functions for successful completion of the fluency domain items within the ACE-III (Laisney et al., 2009; Hsieh et al., 2013).

Non-parametric Mann-Whitney *U* Tests were conducted on each of the domain scores between the PCA and other NDD groups. A statistically significant difference between PCA (median = 25.00) and other NDD (median = 87.50) patients was observed for the visuospatial domain, $U = 1.50$, $p = 0.000$. Differences between groups on the other domains did not reach statistical significance (attention, $U = 31.50$, $p = 0.682$; memory, $U = 33.50$, $p = 0.820$; fluency, $U = 31.00$, $p = 0.682$; language $U = 23.50$, $p = 0.250$).

It can therefore be concluded that no clear differences between PCA and other NDD patients were present on any domain with the exception of visuospatial functions. The groups are clearly heterogeneous, but can be considered adequately matched on the basis of these results. Subsequent analysis on the range of tasks within the screening battery will therefore compare PCA patients with the newly defined 'other NDD' group (including AD and FTD patients).

4.3.2 Memory

Descriptive boxplots are presented in Figure 4.11 below, which demonstrate the scaled scores for patients across the three diagnostic groups on the RBMT-3 immediate recall subtest. Table 4.8 provides a summary of patient performance when compared to the cut-off score for normality for the RBMT-3.

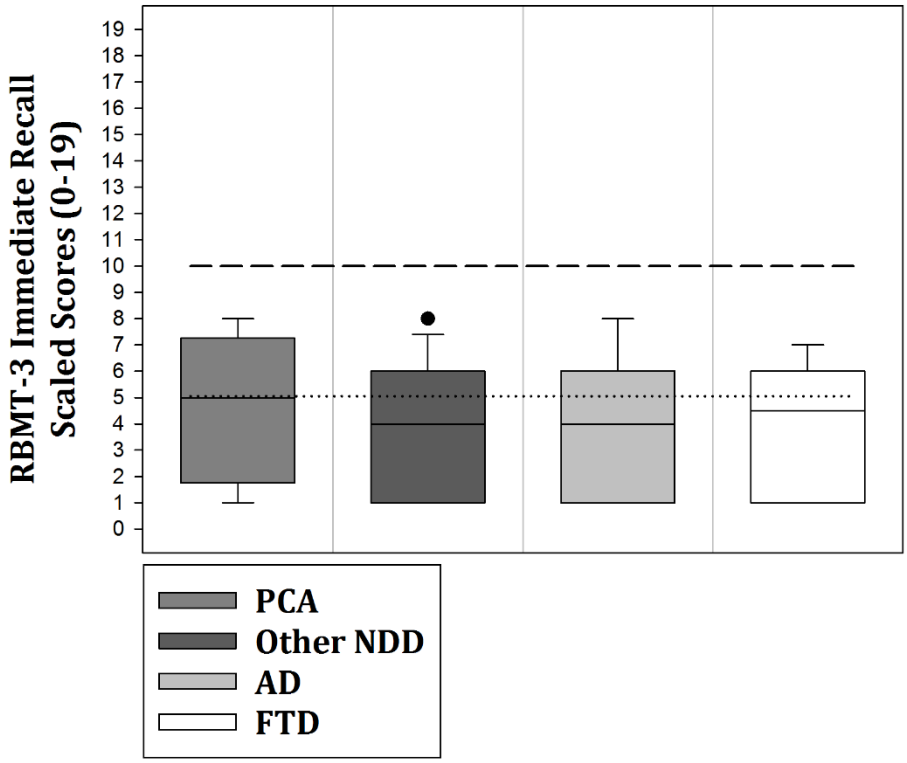


Figure 4.11: Boxplots Illustrating Scaled RBMT-3 Immediate Recall Scores
Note: Outliers are represented as black circles.
Key: — — — represents control mean, · · · · · represents lowest cut off for normal performance

	PCA			Other NDD			AD			FTD		
	N	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**
RMBT-3 Immediate Recall	3	3	1	5	10	1	2	5	1	3	5	-

Table 4.8: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on the RMBT-3 Immediate Recall Subtest.
Note: N = 'normal', greater than the level of lowest cut-off for healthy control performance. A = 'abnormal', below the level of lowest cut-off for healthy control performance, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.
Note: Results from AD and FTD groups are presented for completeness, but are greyed out to indicate that these individual groups were not compared in further analysis.

These plots illustrate the close-to-floor effect of performance across all diagnostic groups on this subtest. Patients do not appear distinguishable based on their diagnostic grouping in terms of performance on this test.

In order to formally analyse this a Mann-Whitney *U* Test was conducted to investigate whether the PCA and other NDD groups differed significantly on immediate recall. PCA patients (median = 5.00) did not differ significantly from other NDD patients (median = 4.00) on immediate recall, $U = 35.00$, $p = 0.367$.

It can be concluded from these results that performance on this subtest was approximately matched between patients in all three diagnostic groups.

4.3.3 Elementary Visual Features

Descriptive boxplots which illustrate the percentage scores across diagnostic groups on measures of elementary visual features is presented in Figure 4.12, below.

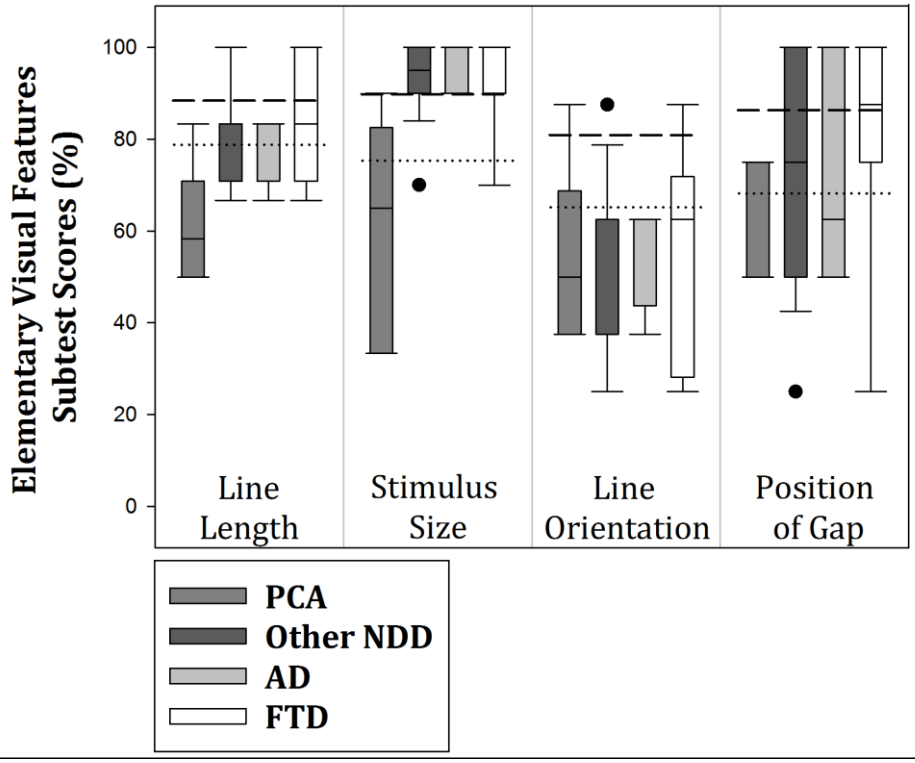


Figure 4.12: Boxplots Illustrating Percentage Scores on Elementary Visual Features Subtests
Note: Outliers are represented as black circles.
Note: Line Length = BORB 2, Stimulus Size = BORB 3, Line Orientation = BORB 4, Position of Gap = BORB 5.
Key: — — — represents control mean, · · · · · represents lowest cut off for normal performance

From these plots it appears that patients do not differ greatly on the line orientation or position of gap subtests; however, PCA patients appear to perform worse on the line length and stimulus size subtests.

In order to address the utility of the elementary visual features domain in identifying PCA patients, a total percentage score was calculated for each patient across the domain. Figure 4.13, below, presents these data. Table 4.9 provides a summary of patient performance when compared to the cut-off score for normality generated for the elementary visual features domain.

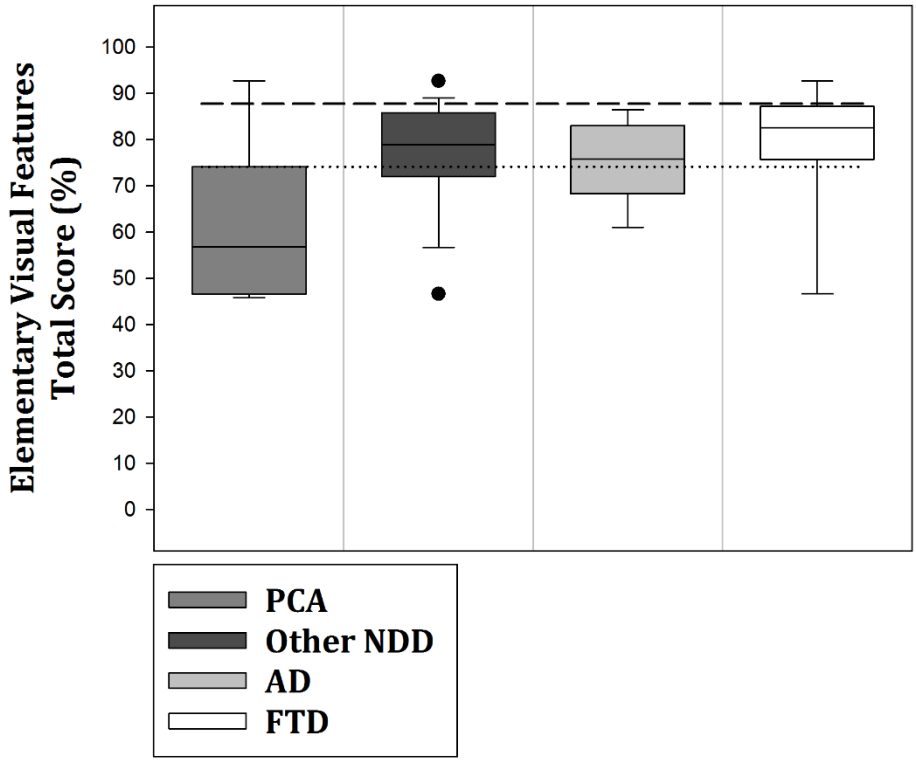


Figure 4.13: Boxplots Illustrating Group Total Percentage Score on Elementary Visual Features Domain
Note: Outliers are represented as black circles.
Key: — — — represents control mean, · · · · · represents lowest cut off for normal performance

	PCA			Other NDD			AD			FTD		
	N	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**
Elementary Visual Features Domain	1	5	-	11	5	-	4	4	-	7	1	-

Table 4.9: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on the Elementary Visual Features Domain

Note: N = 'normal', greater than the level of lowest cut-off for healthy control performance. A = 'abnormal', below the level of lowest cut-off for healthy control performance, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.

Note: Results from AD and FTD groups are presented for completeness, but are greyed out to indicate that these individual groups were not compared in further analysis.

Patients with PCA appear to perform well below the cut off for normal performance within this domain, whereas the majority of patients in the other NDD group perform around the level of healthy controls.

A Mann-Whitney *U* Test was conducted to investigate whether the PCA and other NDD groups differed significantly on elementary visual features domain total score. PCA patients (median = 56.88) differed significantly from other NDD patients (median = 75.83), $U = 21.50$, $p = 0.049$. This domain could therefore be considered effective at discriminating between patients with PCA and patients with other NDDs.

4.3.4 Perception of Multiple Figures

Figure 4.14 below presents the mean reading times for each group across the three conditions considered for analysis.

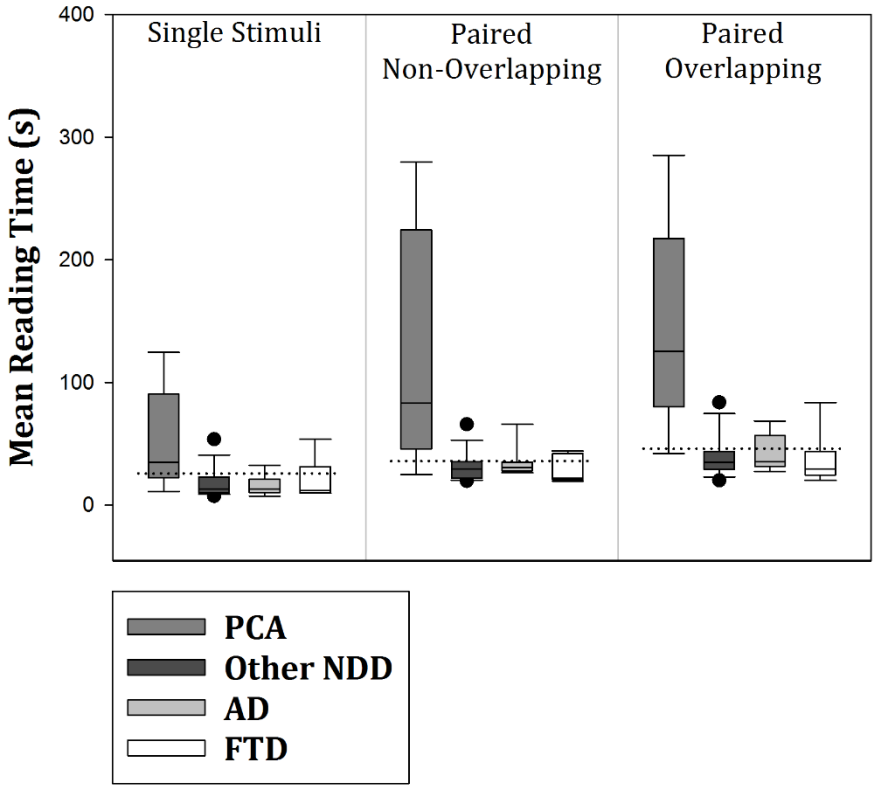


Figure 4.14: Boxplots Illustrating Mean Reading Times (s) for Each Diagnostic Group Across Each Condition

Note: Outliers are represented as black circles.

Key: · · · · · represents mean reading time across each condition for the worst control

	PCA			Other NDD			AD			FTD		
	N	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**
Single Stimuli	1	4	1	12	3	1	7	1	-	5	2	1
Paired Non-Overlapping	1	4	1	12	3	1	7	1	-	5	2	1
Paired Overlapping	1	4	1	13	2	1	6	2	-	7	0	1

Table 4.10: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on Each Perception of Multiple Figures Subtest
Note: N = 'normal', greater than the level of lowest cut-off for healthy control performance. A = 'abnormal', below the level of lowest cut-off for healthy control performance, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.
For this domain: the mean reading time from the worst control was used, and a mean reading time for each condition was calculated. This was used as the cut-off for coding performance. Patients who took longer than this cut off were coded as abnormal, those who took less time were coded as normal.
Note: Results from AD and FTD groups are presented for completeness, but are greyed out to indicate that these individual groups were not compared in further analysis.

Evidently from Figure 4.14 it appears that patients with PCA generally demonstrate much greater mean reading times across all conditions when compared with other NDD patients. Other NDD patients appear to perform just below the level of the mean reading time for the worst control (as reported in Riddoch & Humphreys, 1993). Table 4.10 provides a summary of patient performance when compared to the cut-off scores for normality generated for the perception of multiple figures subtests.

In order to explore group data for indications of simultanagnosia and figure-ground segmentation deficits the CoP and CoO were calculated. These data are presented in Figure 4.15, below. Tables 4.10 and 4.11 provide further summary of patient performance with respect to cut offs for abnormality for the perception of multiple figures subtests, and for CoP and CoO scores.

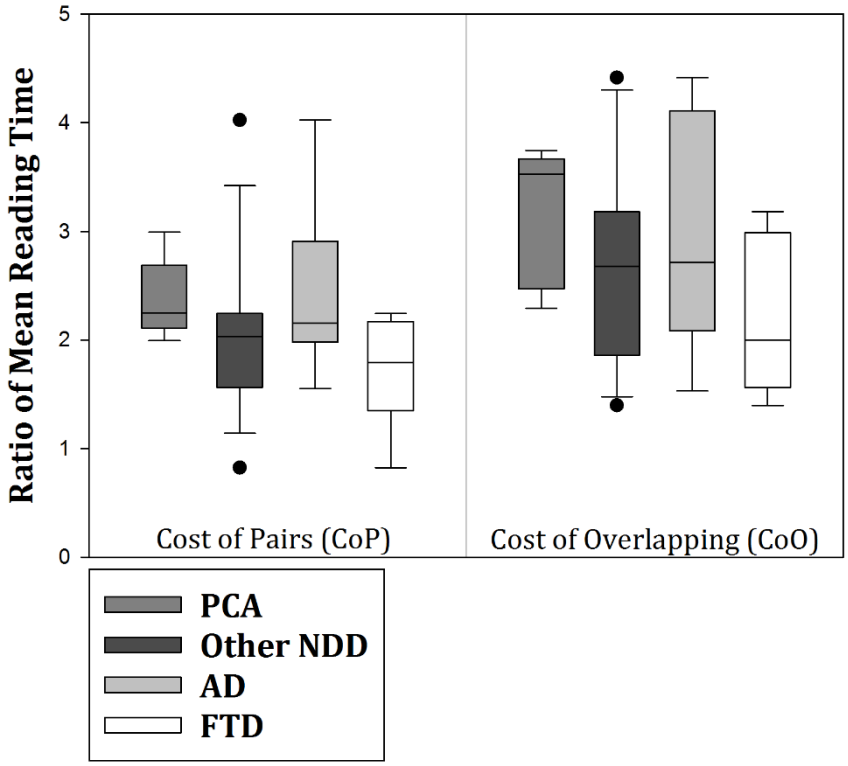


Figure 4.15: Boxplots Illustrating Cost of Pairs (CoP) and Cost of Overlapping (CoO)* for Perception of Multiple Figures.
Note: Outliers are represented as black circles.
*Note: CoP and CoO are calculated as the ratio to the mean single stimuli reading time. See Section 3.1.5.4 for further details.

	PCA			Other NDD			AD			FTD		
	N	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**
CoP	3	2	1	12	3	1	5	3	-	7	0	1
CoO	1	4	1	8	7	1	4	4	-	4	3	1

Table 4.11: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on CoP and CoO
Note: N = 'normal', greater than the level of lowest cut-off for healthy control performance taken as a CoP/CoO ≤ 2.5. A = 'abnormal', below the level of lowest cut-off for healthy control performance taken as a CoP/CoO > 2.5, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest and for whom a CoP or CoO score could not be calculated.
Note: Results from AD and FTD groups are presented for completeness, but are greyed out to indicate that these individual groups were not compared in further analysis.

The prediction was that patients demonstrating symptoms of simultanagnosia would demonstrate a high CoP and an equivalently high CoO. These would not differ significantly if the reading deficit were due to simultanagnosia. In contrast, patients demonstrating symptoms of figure-ground segmentation

deficits would have a small CoP relative to their CoO. It is also notable that the number of stimuli between single and paired conditions are doubled, therefore a ratio around 2 for CoP or CoO would not be indicative of any deficit, as it would reflect only that patients must read twice as many stimuli and therefore are likely to take twice as long between the two conditions.

The boxplots in Figure 4.15 indicate that only PCA patients demonstrate a CoP and CoO of greater than 2, although no clear differences between groups appear to be present. Likewise, the within-group differences between the CoP and CoO ratios appear small.

It was not possible to create a cut-off for normal performance for these ratio scores as the reported worst control score for each subtest was not necessarily from the same individual; generating a ratio from this would be misleading. Therefore, further analysis is restricted to comparison of the patient groups only. Note that Table 4.11 presents proposed cut-offs for abnormality (see Section 4.3.10 for further details).

In order to further analyse differences in CoP and CoO scores, Related Samples Wilcoxon Signed Rank Tests were conducted within-groups between PCA and other NDD on CoP and CoO scores to determine whether these differed significantly. The results indicated that PCA patients did not differ significantly between CoP and CoO, $Z = -1.48$, $p = 0.138$. However, patients in the other NDD group demonstrated a significant difference between CoP and CoO, $Z = -2.95$, $p = 0.003$. This indicates that patients in the other NDD group perform worse on paired-overlapping figures than paired non-overlapping, which may indicate a level of figure-ground segmentation deficit.

Patients in the PCA group had greatly inflated reading times across all conditions. Therefore, interpretation of these results must be cautious. It is possible that as a consequence of these patients' visual deficits they even struggle to read or identify individual figures (in the single stimuli conditions),

which may therefore create a floor effect of performance and render these results too impaired to meaningfully interpret. Indeed, qualitatively, it was noted by the PI that the majority of the PCA patients struggled with identifying single stimuli when completing this task, and patients made a great number of errors when doing so.

Following this analysis, and despite the limitation noted above, further Mann-Whitney *U* Tests were conducted to investigate whether PCA patients and other NDD patients differed significantly on CoP and CoO scores. The results indicated that PCA patients (median = 2.25) did not differ significantly from other NDD patients (median =2.03) on CoP ratio, $U = 22.00$, $p = 0.197$. Likewise, PCA patients (median = 3.53) did not differ significantly from other NDD patients (median = 2.68) on CoO ratio, $U = 25.00$, $p = 0.306$. Therefore, somewhat surprisingly, this subtest was not useful for discriminating between performance of PCA patients and other NDD patients within this sample.

4.3.5 Object Perception

Figure 4.16 below provides descriptive boxplots illustrating the percentage scores for patients across all object perception subtests.

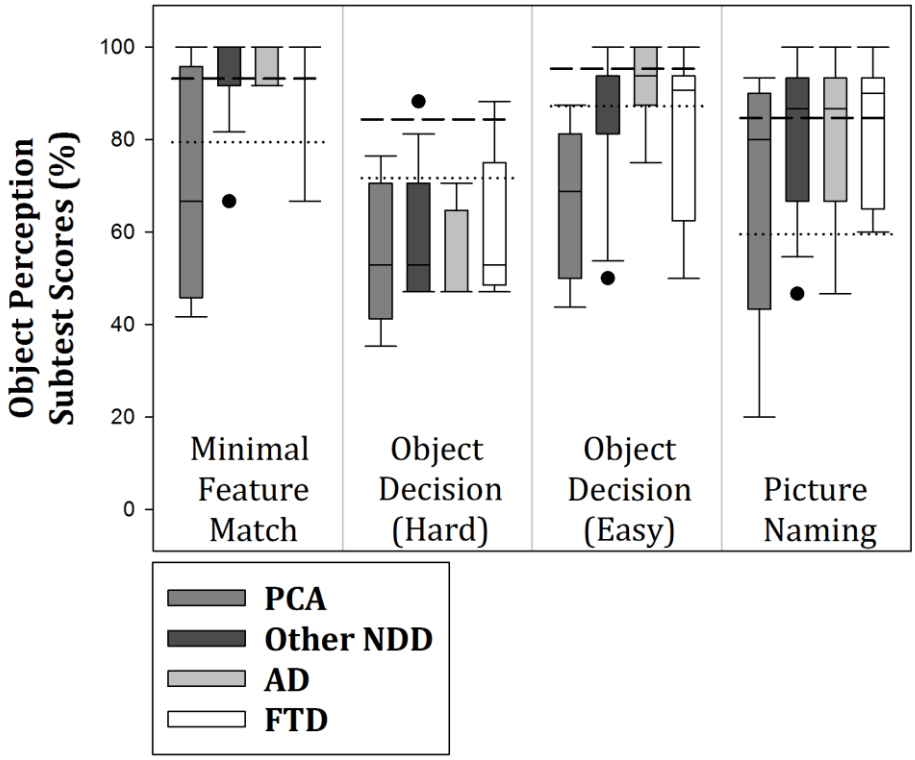


Figure 4.16: Boxplots Illustrating Percentage Scores for Object Perception Subtests
Note: Outliers are represented as black circles.
Note: Minimal Feature Match = BORB 7, Object Decision (Hard) = BORB 10A, Object Decision (Easy) = BORB 10B, Picture Naming = BORB 13.
Key: — — — represents control mean, · · · · · represents lowest cut off for normal performance

From Figure 4.16, above, it appears that performance on the picture naming subtest is relatively similar across groups, with all groups performing close to or just below the level of controls. Performance on the object decision (hard) subtest appears to be largely equivalent across patient groups. Group differences start to emerge on the minimal feature match and object decision (easy) subtests; with PCA patients performing worse than the AD and FTD groups, who appear to be performing at a level close to that of controls. Figure 4.17 and Table 4.12 provide further summaries of performance at the group level.

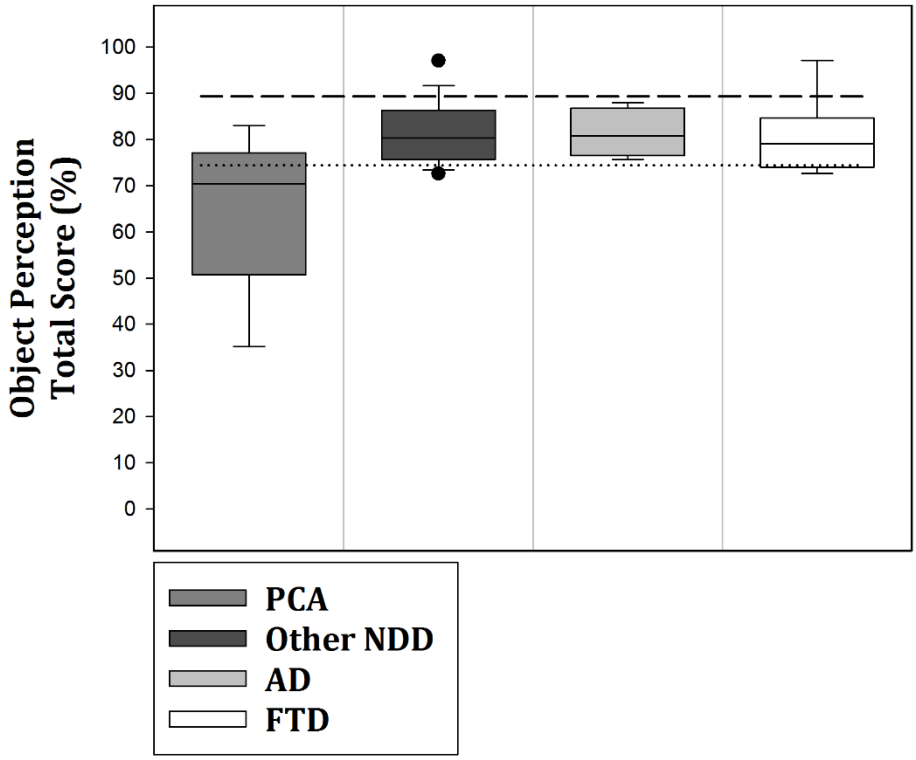


Figure 4.17: Boxplots Illustrating Group Total Percentage Score on Object Perception Domain
Key: — — — represents control mean, · · · · · represents lowest cut off for normal performance

	PCA			Other NDD			AD			FTD		
	N	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**
Object Perception Domain	1	4	1	12	3	1	7	0	1	5	3	-

Table 4.12: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on the Object Perception Domain
Note: N = 'normal', greater than the level of lowest cut-off for healthy control performance. A = 'abnormal', below the level of lowest cut-off for healthy control performance, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.
Note: Results from AD and FTD groups are presented for completeness, but are greyed out to indicate that these individual groups were not compared in further analysis.

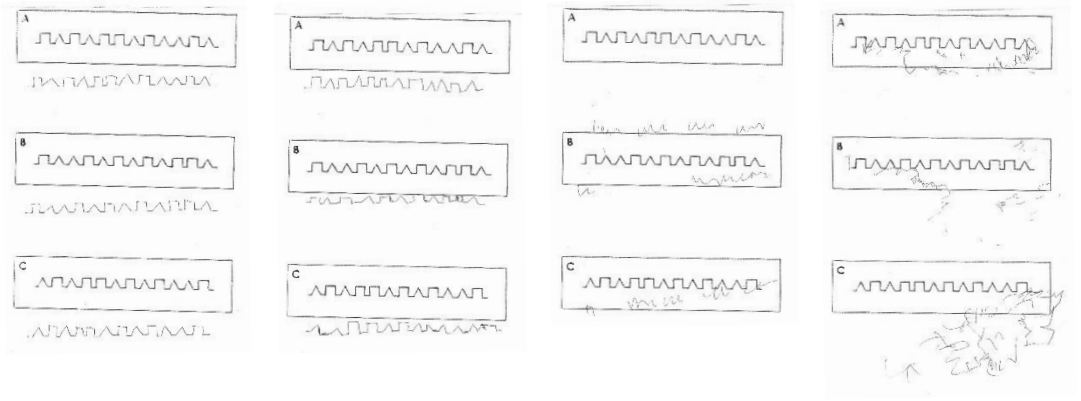
A Mann-Whitney *U* Test was conducted to test whether PCA patients differed significantly from other NDD patients on Object Perception total score, as individual subtests were not analysed for domains (see Section 3.2 for details). PCA patients (median = 70.41) differed significantly from other NDD patients (median = 80.76) on the Object Perception Domain total score, $U = 9.00$, $p =$

0.011. Therefore PCA patients performed worse than other NDD patients within this domain, which may make it a useful identifier for PCA patients when compared with other NDD patients.

4.3.6 Constructional Ability

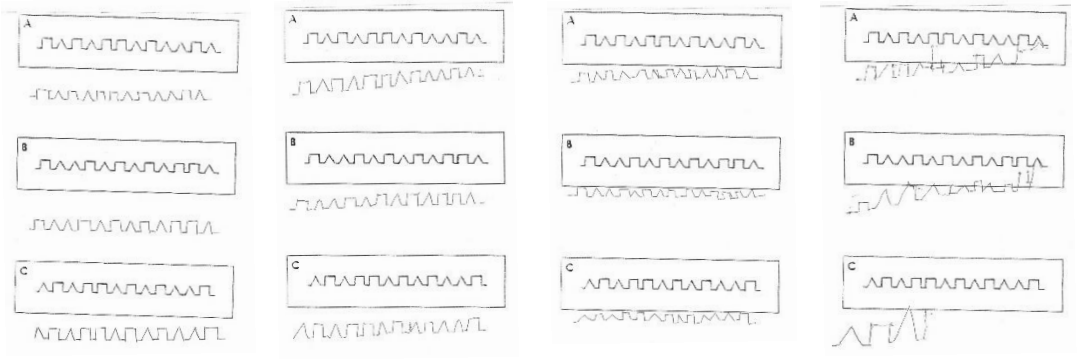
In order to get a general overview of any diagnostic group differences, responses on the M-LAST test were categorized as demonstrating CIB and/or visual-constructional apraxia. Figure 4.18 below presents representative example responses illustrating the characteristics demonstrated, and their associated categorization.

Visual Constructional Apraxia (VCA)



0	1	2	3
Good copy	Recognisable but mildly impaired	Very impaired, barely recognisable	Not recognisable

Closing-in Behaviour (CIB)



0	1	2	3
None evident	Inclined drawing, not touching the stimulus box	Drawing touching the stimulus box	Drawing on top of the figure within the stimulus box

Figure 4.18: Coding System for M-LAST Test and Representative Examples

Figure 4.19 below demonstrates the spread of these data across patient groups (further summarized in Table 4.13). From this it appears that PCA patients demonstrate greater levels of both VCA and CIB compared to other NDD patients. No patients with other NDD demonstrated symptoms of VCA, however this patient group were more varied with regard to CIB. Patients with PCA appear relatively similar in terms of their demonstration of CIB and VCA.

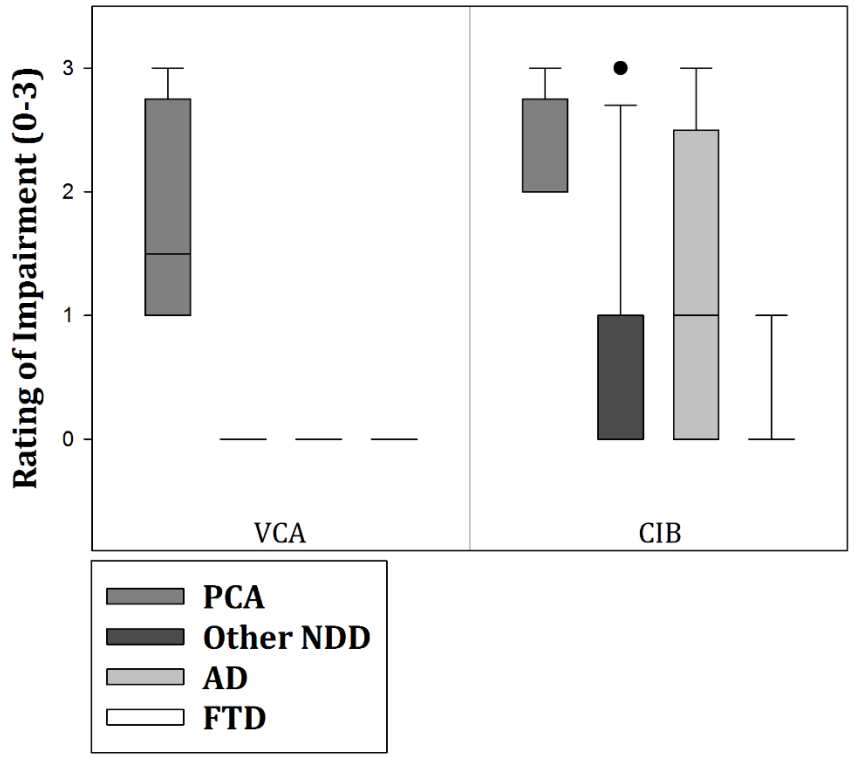


Figure 4.19: M-LAST Performance Ratings for Patients on Visual Constructional Apraxia (VCA) and Closing-in Behaviour (CIB).
Note: Outliers are represented as black circles.

	PCA			Other NDD			AD			FTD		
Severity Rating	VCA	CIB	NC	VCA	CIB	NC	VCA	CIB	NC	VCA	CIB	NC
0	0	0		12	8		5	2		7	6	
1	2	0		0	2		0	1		0	1	
2	1	3		0	1		0	1		0	0	
3	1	1		0	1		0	1		0	0	
			2			4			3			1

Table 4.13: Frequency of Severity of Impairment for VCA and CIB on the Constructional Ability Domain
Note: NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.
Note: Results from AD and FTD groups are presented for completeness, but are greyed out to indicate that these individual groups were not compared in further analysis.

	PCA			Other NDD			AD			FTD		
	N	A	NC	N	A	NC	N	A	NC	N	A	NC
M-LAST VCA	2	2	2	12	0	4	5	0	3	7	0	1
M-LAST CIB	0	4	2	10	2	4	3	2	3	7	0	1

Table 4.14: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on the Constructional Ability Domain
Note: N = 'normal', greater than the level of lowest cut-off for healthy control performance, taken as <2. A = 'abnormal', below the level of lowest cut-off for healthy control performance, taken as ≥ 2, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.
Note: Results from AD and FTD groups are presented for completeness, but are greyed out to indicate that these individual groups were not compared in further analysis.

In order to establish formally whether group differences between PCA and other NDD patients were present for both VCA and CIB; Mann-Whitney *U* Tests were conducted. The results indicated that for PCA patients (median = 1.50) differed significantly from other NDD patients (median = 0.00) on VCA, $U = 0.00$, $p = 0.001$. Likewise, PCA patients (median = 2.00) differed significantly from other NDD patients (median = 0.00) on CIB, $U = 5.00$, $p = 0.020$. These results indicate that PCA patients demonstrate greater severity of both VCA and CIB than other NDD patients.

Table 4.14 presents proposed cut-off scores for normality for the M-LAST test. These scores were not used in the analysis of these results. See Section 4.3.10 for further detail on these proposed cut-offs.

4.3.7 Spatial Attention

4.3.7.1 Line Bisection

Initial analysis on the line bisection task, for the purpose of screening for neglect, is reported in this chapter. For more elaborative analysis see Chapter 5, Section 5.4.2. Within this chapter the dependent variable of interest is the mean response position for each of the two conditions - line and gap.

Figure 4.20 below presents the mean response position across the two conditions for each patient group. Data from 18 age- and sex-matched controls are plotted for comparison. From this figure it seems apparent that patients with PCA make greater rightward errors than other NDD patients, with a greater degree of within-group variability.

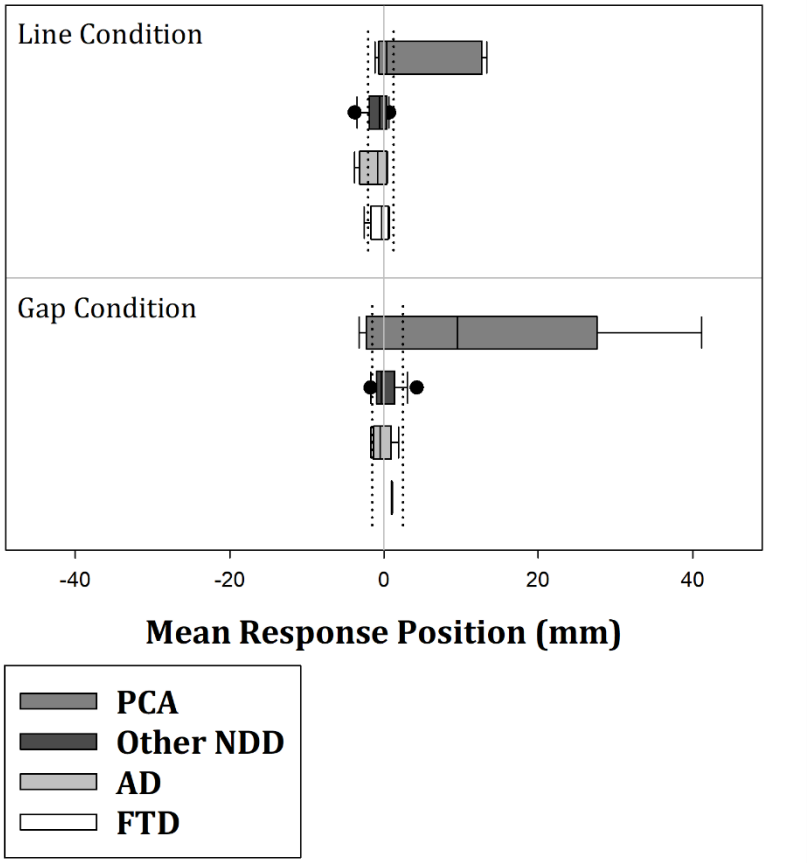


Figure 4.20: Boxplots Illustrating Mean Response Position (mm) on Line Bisection Task.
Note: Outliers are represented as black circles.
Note: 0 is the exact midpoint of the line. Leftward errors are coded as negative, rightward errors are coded as positive.
Key: · · · · · represents upper and lower cutoffs for normal performance.

	PCA			Other NDD			AD			FTD		
	N	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**
Line Condition	3	2	1	11	3	2	5	2	1	6	1	1
Gap Condition	1	3	2	11	3	2	6	1	1	5	2	1

Table 4.15: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on the Line Bisection Test.
Note: N = 'normal', greater than the level of lowest cut-off for healthy control performance. A = 'abnormal', below the level of lowest cut-off for healthy control performance, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.
Note: Results from AD and FTD groups are presented for completeness, but are greyed out to indicate that these individual groups were not compared in further analysis.

From Figure 4.20 it appears that patients with PCA demonstrate a rightward bias in responses in both conditions, with a greater variability of response positions in the gap condition, suggesting that a difference exists between the two tasks. Patients with other NDDs appear to perform in a manner similar to the 18 age- and sex-matched controls. Further elaboration on the differences between the tasks and the specific processing deficits, which may be revealed by each condition, is presented in the discussion section of this chapter. Table 4.15 presents proposed cut-offs for normality, generated from control performance on this task.

Mann-Whitney *U* Tests were conducted to investigate whether PCA patients, other NDD patients and controls differed in mean response positions across the two conditions. The results indicated that PCA patients did not differ from other NDD patients to a level of statistical significance on either condition (line [PCA median = 0.37, other NDD median = -0.60], $U = 17.00$, $p = 0.107$; gap [PCA median = 9.54, other NDD median = -0.39], $U = 25.50$, $p = 0.391$). Similarly, PCA patients did not differ significantly from controls on either condition (line [control median = -0.42], $U = 27.50$, $p = 0.199$; gap [control median = 0.17], $U = 36.00$, $p = 0.538$). Other NDD patients were also not found to differ significantly from controls on either condition (line condition, $U = 106.50$, $p = 0.464$; gap condition, $U = 101.00$, $p = 0.357$). These surprising findings are addressed further in Chapter 5 of this thesis, where alternative metrics for the measurement of impairment on this test are presented, originally proposed by McIntosh, Schindler, Birchall & Milner (2005).

Related Samples Wilcoxon Signed Ranks Tests were conducted in order to address whether within-group differences between the two conditions were detectable. PCA patients did not appear to perform significantly differently between the two conditions, $Z = -0.41$, $p = 0.686$. In contrast: other NDD patients did differ significantly between the conditions, $Z = -2.55$, $p = 0.011$. Control participants were also found to differ significantly between the line and gap conditions, $Z = -3.09$, $p = 0.002$. These results may suggest that, on mean

response position, PCA patients may be equally impaired on both the line and gap tasks, whereas for other NDD patients and control participants – performance on this task differs across conditions.

4.3.7.2 Cancellation

Initial analysis on the cancellation task is reported in this chapter. For more elaborative analysis see Chapter 5, Section 5.5.2. Analysis within this chapter will be on the dependent variable metric most commonly extracted from cancellation tasks; the number of targets omitted.

Figure 4.21 below presents boxplots illustrating the percentage of targets omitted across the two conditions: visible and invisible. Table 4.16 illustrates patient performance with respect to cut-offs for normality generated from control performance. It is immediately apparent from this that patients with PCA omit generally more targets than other patient groups, with an apparent increase in targets omitted in the invisible condition, where no visual feedback of targets touched is given. Patients with other NDDs appear to perform largely at the level of controls in the visible condition, however, responses are more varied in the invisible condition.

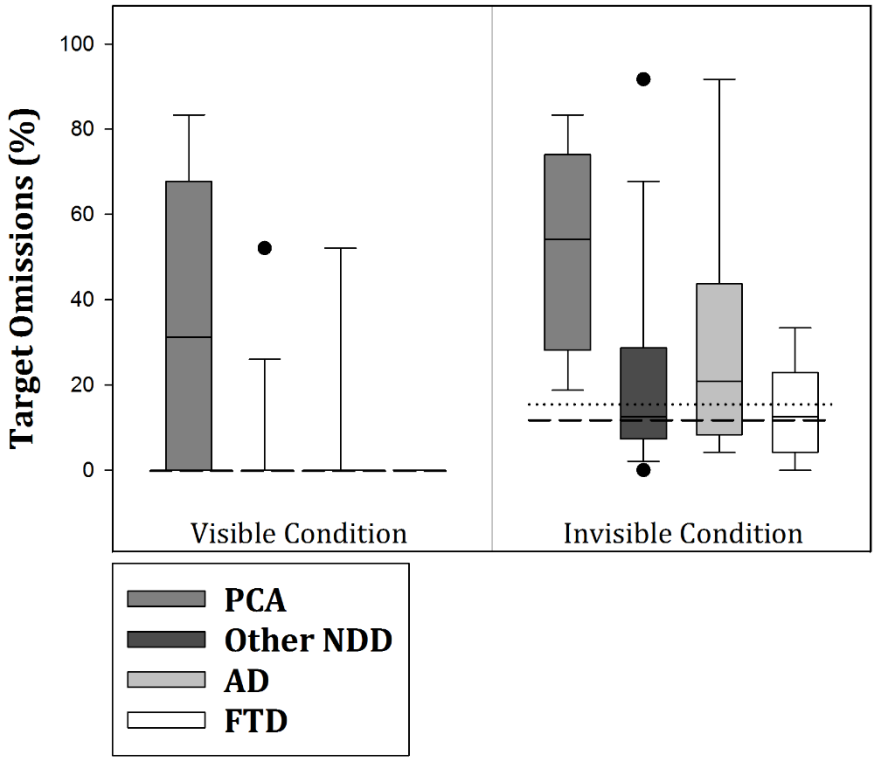


Figure 4.21: Boxplots Illustrating Percentage of Target Omissions on Cancellation Task
Note: Outliers are represented as black circles.
Key: — — — represents age- and sex-matched control mean response, · · · · · represents lowest cut off for normal performance.
Note: All controls within the sample made 0 omissions in the visible condition, therefore no lowest cut off for normal performance could be calculated.

	PCA			Other NDD			AD			FTD		
	N	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**
Visible Condition	2	3		13	1		6	1		7	0	
Invisible Condition	0	5		6	8		3	4		3	4	
			1			2			1			1

Table 4.16: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on the Cancellation Test
Note: 0 = 'normal', greater than the level of lowest cut-off for healthy control performance. 1 = 'abnormal', below the level of lowest cut-off for healthy control performance, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.
Note: Results from AD and FTD groups are presented for completeness, but are greyed out to indicate that these individual groups were not compared in further analysis.

Mann-Whitney *U* Tests were conducted to investigate whether PCA patients, other NDD patients, and controls differed in the percentage of omissions across the two conditions.

In the visible condition, PCA patients (median = 31.25) did not differ significantly from other NDD patients (median = 0.00), $U = 16.50$, $p = 0.09$. PCA patients did differ significantly from controls (median = 0.00) in this condition, $U = 18.00$, $p = 0.046$. Other NDD patients did not differ significantly from controls in this condition $U = 117.00$, $p = 0.750$.

In the invisible condition, PCA patients (median = 54.17) differed significantly from other NDD patients (median = 12.50), $U = 11.00$, $p = 0.026$. This confirms that PCA patients make a greater number of omissions than other NDD patients within this condition. PCA patients also differed significantly from controls (median = 7.29), $U = 6.50$, $p = 0.002$. Other NDD patients, in contrast with the line condition, did differ significantly from controls, $U = 82.50$, $p= 0.099$.

PCA patients were consistently different from controls in their responses across both conditions, making far more omission errors. PCA patients were only found to respond differently from other NDD patients in the invisible condition. This is an interesting finding as it defies the prediction that other NDD patients would be likely to perform at the same level or worse than PCA patients on this condition given the necessity for memory strategies to perform the test successfully.

In order to investigate within-group differences between these conditions Related Samples Wilcoxon Signed Ranks Tests were performed for PCA patients, other NDD patients, and controls. The results indicated that PCA patients did perform significantly differently between the two conditions, $Z = -1.83$, $p = 0.068$. Other NDD patients also differed in their responses between the conditions, $Z = -1.68$, $p = 0.093$. Controls also performed significantly differently between the two conditions, making a greater number of omission errors in the invisible condition, $Z = -3.52$, $p = 0.000$, suggesting a cost associated with no visual feedback.

It should be noted that there is an interesting tension between the ability of this test to discriminate at the individual level when compared to the group level. More than half of PCA patients were impaired on the visible condition, whereas the majority of other NDD patients were unimpaired and yet the statistical analysis at the group level did not detect differences to a satisfactory level of significance. The low power associated with this analysis will certainly impact this finding.

These initial analyses provide some insight into the potential discriminable ability of this test between PCA and other NDD patients – suggesting that the two groups of patients differ significantly on their performance on the invisible condition. Additional dependent variables which may give greater insight into more complex patterns of behaviour relating to visual and attentional deficits are addressed in detail within Chapter 5.

4.3.8 Executive Control of Attention

Descriptive boxplots illustrating the spread of the data are presented in Figure 4.22, below.

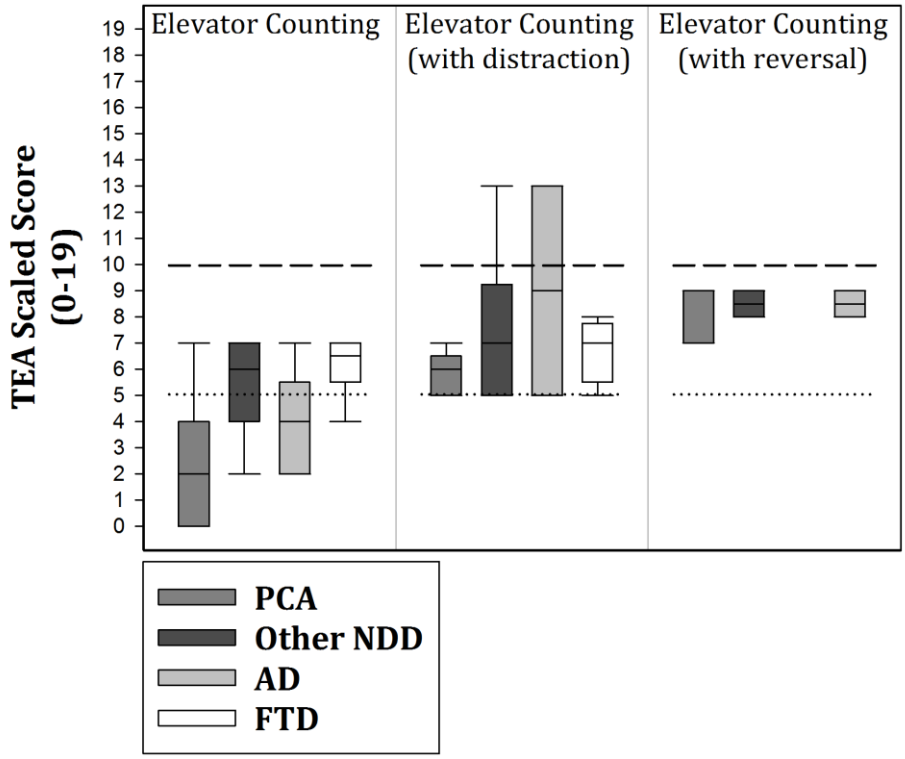


Figure 4.22: Boxplots Illustrating Scaled TEA Scores
Note: Outliers are represented as black circles.
Key: — — — represents control mean, · · · · · represents lowest cut off for normal performance

	PCA			Other NDD			AD			FTD		
	N	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**
Elevator Counting	1	5	-	6	5	5	1	4	3	5	1	2
Elevator Counting (with distraction)	3	2	1	2	4	10	1	1	6	1	3	4
Elevator Counting (with reversal)	3	0	3	2	-	14	-	-	8	2	-	6

Table 4.17: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on the Object Perception Domain
Note: - is entered where no patients in this group fulfilled the condition due to non-completion of the test.
Note: N = 'normal', greater than the level of lowest cut-off for healthy control performance. A = 'abnormal', below the level of lowest cut-off for healthy control performance, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.
Note: Results from AD and FTD groups are presented for completeness, but are greyed out to indicate that these individual groups were not compared in further analysis.

This subtest was challenging for patients, therefore there was a high attrition rate between conditions, as many patients were not able to progress beyond the practice items. Notable from Figure 4.22 is the finding that, for those patients who were able to progress beyond the first condition and complete the increasingly more complex conditions, their performance was within normal limits (see also Table 4.17). This is perhaps not surprising, but it does suggest a sharp drop off between those who can and those who cannot complete the test. In other words, those who started the 'elevator counting with distraction' and 'elevator counting with reversal' subtests were generally able to complete them successfully with relatively few errors.

A Mann-Whitney *U* Test was conducted to establish whether PCA patients differed significantly from other NDD patients on the 'elevator counting' subtest. It was not possible to statistically analyse the further two conditions 'elevator counting with reversal' and 'elevator counting with distraction' as too few patients completed these subtests.

A statistically significant difference between performance on the 'elevator counting' subtest was present between PCA patients (median = 2.00) and other NDD patients (median = 4.00), $U = 13.00$, $p = 0.048$. Therefore PCA patients performed significantly worse than other NDD patients on this subtest. This is an interesting finding as it suggests that PCA patients may experience deficits in other attentional domains, not limited only to visual attention as previously suggested.

Data were available from 18 healthy age- and sex-matched controls (see Chapter 5, Section 5.1.3.2 for details on this sample) therefore further analysis was completed using Mann-Whitney *U* Tests in order to establish whether PCA and other NDD patients differed from this control sample on the 'elevator counting' subtest. The results indicated that PCA patients (median = 2.00) differed significantly from controls (median = 7.00) on the 'elevator counting' subtest, $U = 9.50$, $p = 0.001$. Likewise, other NDD patients (median = 6.00)

differed significantly from controls on this subtest, $U = 39.00$, $p = 0.006$. These results indicate that patients with other NDDs do perform just below the level of controls with a median score just below the maximum attainable score of 7. However, patients with PCA are significantly more impaired when compared to other NDD patients – and perform much worse than control participants in this condition.

4.3.9 Additional Tests

4.3.9.1 Alexia

Alexia recordings were assessed and errors were coded according to the criteria outlined in Table 4.18 below.

Error Code	Description
Misreading	A mispronounced, uncorrected work
Omission	A word that is not read and is missed out entirely
Insertion	A word that is added which is not present in the text

Table 4.18: Error Coding System for Alexia Passage Test

Errors were coded as left sided or right sided according to the criteria detailed in Figure 4.6, in Section 4.1.5.9.

A total of 24 patients (12 female, 12 male; mean age at time of testing 64.78 (SD = 6.27)) completed this assessment. Initial descriptive statistics describing these data are presented in Figure 4.23 and Figure 4.24, below.

Figure 4.23 below illustrates the lateralisation of reading errors.

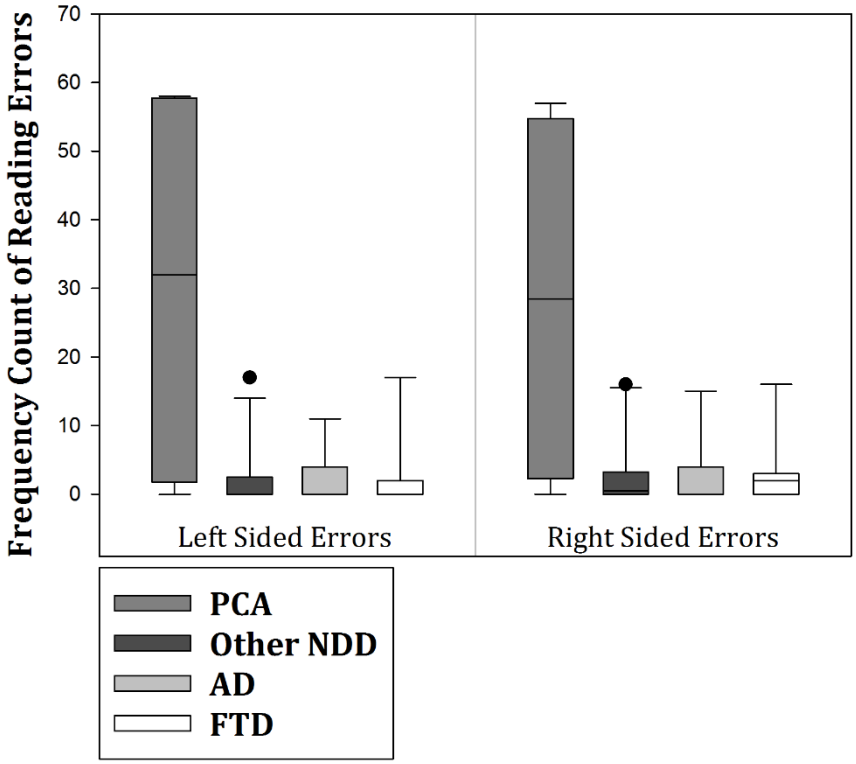


Figure 4.23: Boxplots Illustrating Lateralisation of Reading Errors on Alexia Passage
Note: Outliers are represented as black circles.

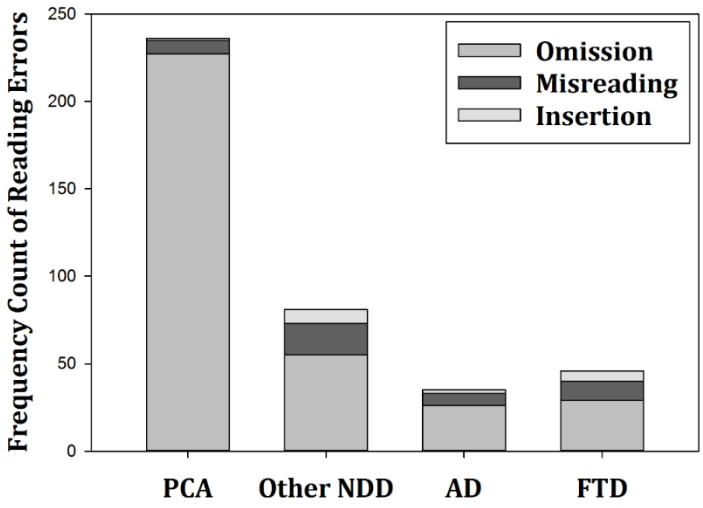


Figure 4.24: Stacked Bar Chart Illustrating Rates of Different Error Types on Alexia Passage

A Mann-Whitney *U* Test was conducted on the total number of errors between the PCA (median = 60.50) and other NDD (median = 1.50) group. No significant difference between groups was observed, $U = 13.00$, $p = 0.127$. Further Mann-Whitney *U* Tests were run on each of the additional dependent variables recorded from this assessment between the PCA and other NDD groups. The frequency of errors of omission was significantly different between PCA (median = 56.00) and other NDD (median = 0.00) patients, $U = 11.50$, $p = 0.079$. Group differences on the other dependent variables did not reach an acceptable level of statistical significance (leftward errors, $U = 12.00$, $p = 0.101$; rightward errors, $U = 12.50$, $p = 0.101$; total errors of misreading $U = 24.50$, $p = 0.721$; total errors of insertion $U = 28.00$, $p = 1.000$). Very few errors of insertion were made therefore testing for differences between groups on the frequency of these errors was not reliable.

The results of this analysis therefore suggest that errors of omission may be a useful way to distinguish between patients with PCA or other NDDs. The fact that total errors did not reach a satisfactory level of statistical significance despite clear between-group differences may be a result of the low power of this analysis. Functionally, errors of omission may signify simultanagnosia-like symptoms in PCA patients – although the possibility that these errors may be due to an acquired dyslexia or attentional deficit other than simultanagnosia should be acknowledged.

4.3.9.2 Finger Agnosia

A total of 24 patients (12 female, 12 male; mean age at time of testing 64.78 (SD = 6.27)) completed this assessment, and 18 age- and sex-matched controls (10 female, 8 male; mean age at time of testing 65.43 (SD = 6.36).

Cut-off scores for normality were generated using results from the age- and sex-matched controls, following the formulae outlined in Section 4.2.1.

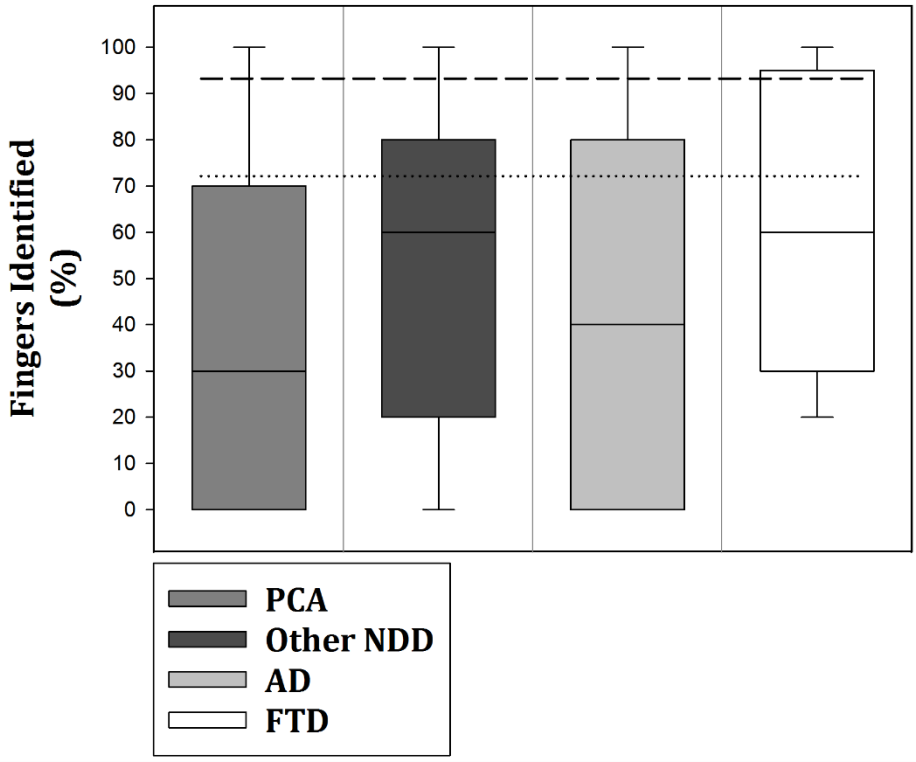


Figure 4.25: Boxplots Illustrating Percentage of Fingers Identified
Note: Outliers are represented as black circles.
Key: — — — represents age/sex matched control mean, · · · · · represents lowest cut off for normal performance

	PCA			Other NDD			AD			FTD		
	N	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**
Finger Agnosia	1	5	-	5	10	1	2	5	1	3	5	-

Table 4.19: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on the Finger Agnosia Test
Note: N = 'normal', greater than the level of lowest cut-off for healthy age/sex matched control performance. A = 'abnormal', below the level of lowest cut-off for healthy age/sex matched control performance, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.
Note: Results from AD and FTD groups are presented for completeness, but are greyed out to indicate that these individual groups were not compared in further analysis.

Figure 4.25 and Table 4.19 above demonstrate that the majority of patients, regardless of diagnostic group, appeared to score below the lowest cut-off for normality on this subtest, suggesting a high level of finger recognition deficit.

In order to test whether group differences were present on percentage finger recognition score between PCA and other NDD patients a Mann-Whitney *U* Test was conducted. PCA patients (median = 30.00) did not differ significantly from other NDD patients (median = 40.00) on number of fingers identified, $U = 32.50$, $p = 0.340$. Therefore PCA patients and other NDD patients did not differ significantly on the level of finger recognition.

In order to gain further insight into this, results were analysed from the 18 age- and sex-matched controls. Mann-Whitney *U* Tests were conducted to compare patients with PCA and patients with other NDDs to this control population. Perhaps unsurprisingly, the results indicated that patients with PCA (median = 40.00) performed significantly differently from controls (median = 100.00) on this test, $U = 12.00$, $p = 0.012$. Likewise, patients with other NDDs (median = 60.00) also performed significantly differently from controls $U = 34.00$, $p = 0.000$. It can therefore be tentatively concluded that all patients, regardless of diagnosis, demonstrated a degree of finger agnosia.

4.3.9.3 TROG

A total of 24 patients completed this task (12 female, 12 male; mean age at time of testing 64.78 (SD = 6.27)). The dependent variables measured in this task were number of items correct (maximum 80) and number of blocks correct (maximum 20).

Control data from Croot, Hodges & Patterson (1998) were used for comparison. The control sample comprised 20 age- and education-matched controls to the authors' sample of 46 patients diagnosed with probable dementia of the Alzheimer's type (16 female, 4 male; mean age 68.7 (SD = 7.5)). On items correct, controls were reported to score between 75 and 80 (93.75-100%), and on blocks correct, controls results ranged from 17 to 20 (85-100%).

Figure 4.26, below, presents descriptive boxplots demonstrating performance on the TROG at the item and block level across each diagnostic group. Table 4.20 further summarizes these data with respect to cut-offs for normality generated from Croot, Hodges & Patterson (1998).

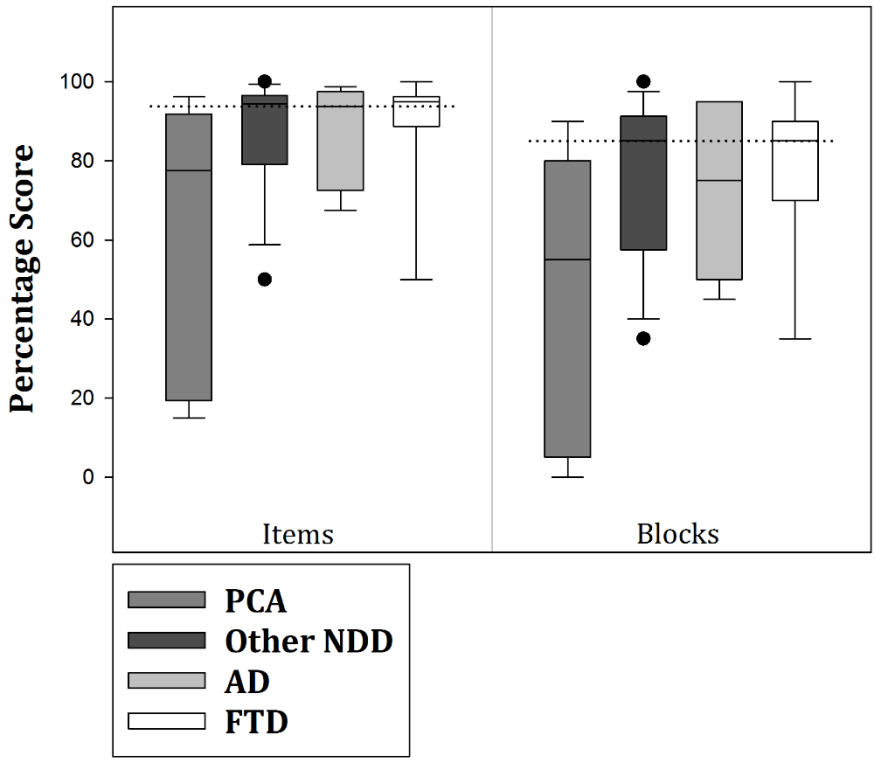


Figure 4.26: Descriptive Boxplots of Performance on the TROG at the Block and Item Level
Note: Outliers are represented as black circles.
Key: · · · · · represents lowest cut off for normal performance, taken as the lowest value of the range reported in Croot, Hodges & Patterson (1998).

	PCA			Other NDD			AD			FTD		
	N	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**	**N**	**A**	**NC**
TROG Items	1	4		8	6		4	3		4	3	
TROG Blocks	1	4		8	6		3	4		5	2	
			1			2			1			1

Table 4.20: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on the Finger Agnosia Test
Note: N = 'normal', greater than the level of lowest cut-off for healthy control performance. A = 'abnormal', below the level of lowest cut-off for healthy control performance, NC = 'non-completers', indicating the number of patients within the full sample who did not complete

the subtest. Cut-off taken as the lowest value of the range reported in Croot, Hodges & Patterson (1998).

Mann-Whitney *U* Tests were conducted on both the percentage of items correct and the percentage of blocks correct between the PCA and other NDD group. A significant difference between PCA patients (median = 55.00) and other NDD patients (median = 85.00) was observed on the percentage of blocks correct, $U = 14.50$, $p = 0.056$. Likewise, a significant difference between the PCA (median = 77.50) and other NDD (median = 95.63) patients was observed for the percentage of items correct, $U = 13.50$, $p = 0.044$.

These results indicate that PCA patients make more errors at the item level and fail more on the block level when compared to the other NDD patients in this sample. PCA patients certainly took considerably longer than other NDD patients to complete this task, often ruminating over one image out of the four and seeming to guess fairly often at the answer. The significant difference between the two groups on items correct may reflect this greater preponderance for guessing within the PCA group. It is therefore perhaps unsurprising that PCA patients performed worse than other NDD patients at the block level, too. The discontinuation rule, which applied to this task, was that more than 50% errors on three consecutive blocks would lead to the termination of the task. Therefore, due to the high level of errors within each block for PCA patients there was a high discontinuation rate. Completion of this task within this patient group is inherently difficult due to the visual symptoms that patients with PCA typically experience, therefore diagnostically the TROG may be of limited utility.

4.3.10 Rates of Impairment

The initial aim of this screening battery was to establish the sensitivity and specificity of the screening tests to discriminate PCA patients from patients with other NDDs. Given the limited patient numbers available: conducting sensitivity and specificity analyses was considered inappropriate, as these analyses may result in misleading claims given the high proportion of PCA to other NDD

patients in this sample. In the present sample, PCA is much more common (22.22%) than in typical samples of patients being screened for dementia (where the prevalence is estimated to be around 10%) (Crutch, Lehmann, Schott, Rabinovici, Rossor & Fox, 2012; Alzheimer's Association, 2017). Similarly, overall diagnostic accuracy (as a measure for evaluating a clinical test) is widely considered problematic given the reliance on prevalence for its calculation, and warnings against its use are common as a result (Alberg, Park, Hager, Brock & Diener-West, 2004; Shapiro, 1999).

However, sensitivity, specificity, and diagnostic accuracy calculations were used to determine cut-offs for normality for tests where no cut-offs were provided. The following standard definitions were used:

$$Sensitivity = \frac{True\ Positive}{(True\ Positive + False\ Negative)}$$

$$Specificity = \frac{True\ Negative}{(True\ Negative + False\ Positive)}$$

$$Diagnostic\ Accuracy = \frac{(True\ Positive + True\ Negative)}{(True\ Positive + False\ Positive + False\ Negative + True\ Negative)}$$

For clarity, the definitions of each term for this calculation are provided in Table 4.21 below.

Term	Definition
True Positive	PCA patients identified as impaired
True Negative	Other NDD patients identified as unimpaired
False Positive	Other NDD patients identified as impaired
False Negative	PCA patients identified as unimpaired

Table 4.21: Terms and Definitions for Sensitivity, Specificity, and Diagnostic Accuracy Analysis

Table 4.22, below, presents details on the number and percentage of patients who were identified as impaired on each task. These calculations were used to give an overview of rates of impairment on each task, in lieu of sensitivity and specificity calculations.

Domain	Subtest	Condition / Measure	Rate of Impairment			
			PCA		Other NDD	
			n	%	n	%
1. Memory	RBMT-3		3	50.00	10	66.66
2. Elementary Visual Features	DTS		5	83.00	5	31.25
3. Perception of Multiple Figures	BORB Subtest 6					
		CoP	2	40.00	3	20.00
		CoO	4	80.00	7	46.66
4. Object Perception	DTS		4	80.00	3	20.00
5. Constructional Ability	M-LAST					
		VCA	2	50.00	0	00.00
		CIB	4	100.00	9	60.00
6. Spatial Attention	Cancellation					
		Visible	3	60.00	1	7.14
		Invisible	5	100.00	8	57.14
	Line Bisection					
		Line	2	40.00	3	21.43
		Gap	3	75.00	3	21.43
7. Executive Control of Attention	Elevator Counting		5	83.33	5	45.45
8. Additional Tests	Alexia passage		ND	ND	ND	ND
	Finger Agnosia					
	TROG					
		Blocks	4	80.00	6	42.85
		Items	4	80.00	6	42.85

Table 4.22: Rates of Impairment for PCA and other NDD Patients
Note: DTS = 'Domain Total Score', ND = not determined, as no cut-offs for normality were available.

For domain 3 (perception of multiple figures) and domain 5 (constructional ability) no cut-offs for abnormality were available, based on existing healthy

control data. Therefore calculations of impairment were conducted for differing abnormality cut-offs in order to determine what the optimal cut-off for normality would be for the present sample. Further details on these calculations are presented below.

For the perception of multiple figures domain, initial analyses were carried out using a CoP or CoO score of greater than two to indicate abnormality, with cost scores of less than two being coded as within normal healthy limits. However, adjusting the cut-off to 2.5 (a CoP/CoO score of greater than 2.5 to indicate abnormality, and less than or equal to 2.5 to be coded as within normal limits) led to a better balance between sensitivity and specificity scores for this subtest. Table 4.23 below presents the sensitivity, specificity and diagnostic accuracy scores for the CoP and CoO using different cut-offs for abnormality. Therefore it was determined that a cut-off for normality at the level of 2.5 was appropriate for both the CoP and CoO.

Perception of Multiple Figures Abnormality Cut-Off	Condition / Measure	Sensitivity (%)	Specificity (%)	Diagnostic Accuracy (%)
2.0				
	CoP	80.00	40.00	50.00
	CoO	100.00	26.67	45.00
2.5				
	CoP	40.00	80.00	70.00
	CoO	80.00	53.33	60.00
3.0				
	CoP	00.00	86.67	65.00
	CoO	60.00	73.33	70.00

Table 4.23: Sensitivity, Specificity, and Diagnostic Accuracy Calculations for BORB Subtest 6 Using Adjusted Abnormality Cut-Offs
Note: Abnormality Cut-Off refers to coding of participants as abnormal (> the abnormality cut-off score for CoP or CoO) or within normal limits (≤ the abnormality cut-off score for CoP or CoO).

Similarly, in order to determine the optimal cut-off for normality for the M-LAST subtest, a series of calculations was conducted using different abnormality cut off scores (Table 4.24). An abnormality cut-off of two was accepted (whereby a level of VCA or CIB of less than two was considered within normal limits, and a score of greater than or equal to two on both measures was coded as abnormal).

M-LAST Abnormality Cut-Off	Condition / Measure	Sensitivity (%)	Specificity (%)	Diagnostic Accuracy (%)
1.0				
	VCA	100.00	100.00	100.00
	CIB	100.00	66.67	75.00
2.0				
	VCA	50.00	100.00	87.50
	CIB	100.00	83.33	87.50
3.0				
	VCA	25.00	100.00	81.25
	CIB	25.00	91.67	75.00

Table 4.24: Sensitivity, Specificity, and Diagnostic Accuracy Calculations for M-LAST Using Adjusted Abnormality Cut-Offs
Note: Abnormality Cut-Off refers to coding of participants as abnormal (≥ the abnormality cut-off score) or within normal limits (< the abnormality cut-off score).

The use of an abnormality cut-off of two, particularly for CIB, is supported theoretically within the literature. One large-scale retrospective study of CIB, for example, defines three variants of CIB: overlap-CIB, near-CIB, and no CIB (Ambron, McIntosh, Allaria & Della Sala, 2009). According to the scoring criteria presented in Figure 4.18, Section 4.3.6 of this chapter, these variants of CIB correspond to scores of greater than or equal to two for overlap-CIB, a score of one for near-type CIB, and a score of zero when there is no CIB (Ambron et al., 2009). There is a degree of subjectivity in the scoring of near-type CIB, whereas overlap-type CIB is far more objective in measurement (in other words, it is clear when a copy is encroaching on or on top of the figure, whereas it is less clear to determine when a copy is inclined). Overlap-type CIB is objectively associated with attentional and visuospatial impairment, therefore the cut off of two for abnormality seems to be a reasonable assertion (Ambron et al., 2009).

4.4 Discussion

A diverse battery of assessments with three main aims was designed. Primarily this screening battery was intended to establish the sensitivity and specificity of certain screening tests to discriminate PCA patients from patients with other NDDs. The secondary aim of this study was to identify whether patients with other NDDs demonstrated deficits on the assessments, which were specific to

early visual function as this is an area which has not been addressed previously in the literature. The third aim of this study was to identify patients within the sample who demonstrated evidence of visual or visuomotor impairment, which may then be a useful predictor of their performance in subsequent, more detailed, lab-based investigations.

The aims of this screening battery were adjusted somewhat during the course of testing as, early on, it became clear that due to the time the assessments were taking, and the limited number of patients it was possible to recruit into the study, it was necessary to invite all patients from Phase 1 into Phase 2 (the lab-based assessments), rather than just those patients showing impairment on the screening battery. This policy was pursued in order to account for the predicted attrition rate of approximately 30% of patients between phases and was intended to allow for as many patients as possible to come to the lab for detailed follow-up (Gustavson, von Soest, Karevold & Røysamb, 2012). Therefore the initially stated third aim of this study is not discussed further as it no longer has relevance. However, the predictive nature of performance from the screening phase on subsequent lab-based assessments is addressed in Chapter 7.

Similarly, instead of calculating the sensitivity, specificity, and diagnostic accuracy for each assessment – which would be misleading when calculated from a sample with a high base rate of PCA – such as the present one; percentage of patients impaired for each domain was calculated in order to provide an accurate reflection for the present sample.

4.4.1 Diagnostic Utility of Tests for Discriminating PCA from Other NDDs

The initial group-level analyses of the screening subtests, included in this battery, highlighted which cognitive domains best distinguished patients with PCA from patients with other NDDs within this sample. PCA patients performed at a level significantly worse than patients with other NDDs within the following domains: elementary visual features (domain total score), perception of

multiple figures (mean total reading time for single, paired non-overlapping and paired overlapping stimuli), object perception (domain total score), constructional ability (greater levels of VCA and CIB), spatial attention (cancellation task – visible condition), executive control of attention (TEA – 'elevator counting' condition), and within the additional tasks of alexia (greater total errors of omission) as well as the TROG (items and blocks). On all of these tasks, the majority of patients with other NDDs performed at a level above the lowest cut-off for healthy control performance – suggesting that these tasks target symptoms associated more specifically with PCA.

4.4.2 Frequency of Visual Symptoms in Patients with Other NDDs

There were a number of tests in which a significant level of impairment was observed for patients with other NDDs which addresses the initially stated second aim of this study – to investigate the frequency of primary visual symptoms in patients with other NDDs. Patients with other NDDs demonstrated deficits within the following domains: perception of multiple figures (a significantly greater CoO to CoP score), spatial attention (a significantly greater frequency of errors of omission when compared to age- and sex-matched controls on the cancellation task – invisible condition), executive control of attention (performing significantly worse than age- and sex-matched controls on the TEA – 'elevator counting' subtest), and on the additional test of finger agnosia (recognising significantly fewer fingers than age- and sex-matched controls, with around 67% of other NDD patients performing below the cut off for normal performance).

The finding of a greater CoO to CoP score is suggestive of a figure-ground segmentation deficit in the other NDD patients. Published quantitative investigations into figure-ground perceptual deficits within the dementia population are scarce. Studies, which do address this visual ability, demonstrate evidence of figure-ground segmentation deficits within patients with LBD, but show little agreement as to the observed frequency of such symptoms in

patients with other forms of dementia (Mendez, Mendez, Martin, Smyth & Whitehouse, 1990; Mendez, Thomsak & Remler, 1990; Calderon et al., 2001; Xuemei, Rastogi, Gibbons & Chaudhury, 2014; Sells & Larner, 2011). Therefore the findings of the present study may serve to provide some evidence of figure-ground segmentation deficits in dementia other than LBD. Observing possible figure-ground discrimination deficits in these patients would predict that these patients may experience a range of visual problems in daily life. It was beyond the scope of the present study to systematically investigate – either through assessment of the patient or through consultation with caregivers or family members – whether these patients experienced concurrent visual problems in daily life. Sight loss is a common consequence of ageing, but a recent large-scale study conducted by Bowen et al. (2016) addressed the question specifically about the prevalence of visual impairment in people with dementia. The report found that visual impairment (as measured by visual acuity) was disproportionately higher in people with dementia living in care homes when compared to those living at home (Bowen et al., 2016). It is interesting to note that, despite this being a large-scale multi-centre study, no attempt was made to explore visual symptoms beyond visual acuity, for instance prevalence of optic ataxia, simultanagnosia, or visual neglect. Further investigation testing for cortical visual symptoms such as those listed above may reveal that the patients with dementia living in care homes demonstrate higher levels of these symptoms than dementia patients living independently; this would account, in part, for their difficulties with everyday activities. Of course, this is a rather general statement, but poses an interesting question nonetheless. There is scant systematic research investigating visual symptoms of any kind within the dementia population, most likely due to the overwhelming impact that these patients' other neurocognitive symptoms (such as memory, executive control, and language) have on their quality of life and that of their families. As discussed in the introduction to this chapter, visual problems are seldom rigorously assessed by the cognitive screening batteries typically applied to the assessment of these populations. Visual impairment is associated with greater difficulties in activities of daily living, increased rates of depression, social

isolation, and indeed falls (Meehan & Shura, 2016). A systematic investigation into the prevalence of visual impairment, beyond simply visual actuity, in patients with neurodegenerative diseases, manifested in difficulties with everyday activities, may therefore be an important area for future research.

Considering the test of finger agnosia: observing a deficit in the patients with other NDDs within this sample is supported by a previous investigation of finger agnosia within dementia patients (Shenal, Jackson, Crucian & Heilman, 2006). Finger agnosia is a symptom commonly associated with cortical dementias, and has been suggested as a predictive metric of decline (Kramer & Duffy, 1996; Rasmusson, Carson, Brookmeyer, Kawas & Brandt, 1996), however – as with figure-ground segmentation – there is little published research addressing the frequency of finger agnosia specifically in dementia patients other than those with PCA. Finger agnosia is one of four symptoms of Gerstmann's syndrome (which also includes acalculia, left-right disorientation and agraphia) (Heimburger, Demyer & Reitan, 1964; Roux, Boetto, Sacko, Chollet & Trémoulet, 2003). These results therefore present some evidence to suggest that finger agnosia may be prevalent in other dementias, perhaps suggesting that elements of Gerstmann's syndrome may be demonstrable in dementia other than PCA.

Finding evidence of CIB in patients with other NDDs is supported by existing literature (Ambron, Allaria, McIntosh & Della Sala, 2009; McIntosh, Ambron, Della Sala, 2008; Kwak, 2004; Chin et al., 2005; Serra, Fadda, Perri, Caltagirone & Carlesimo, 2010). Although classically considered a form of constructional apraxia, the results of the present study (where no constructional apraxia was observed in this group) and additional evidence from recent research (Ambron et al., 2009) suggests that CIB and VCA may not have such a simple relationship and may be driven by separate cognitive factors. There are two prevailing hypotheses as to the mechanism from which CIB is observed. The first is the compensation hypothesis, which suggests that CIB is the result of a strategy adopted in order to overcome basic visuospatial dysfunctions, which are involved in the primary visuoperceptual analysis of a scene (Serra et al., 2010).

The second is the attraction account, which suggests that CIB is a consequence of a "primitive default behaviour" (Mcintosh et al., p.376) whereby the hand is automatically drawn towards the focus of visual attention. The overall results of this screening battery – which have demonstrated relatively low levels of visual dysfunctions in the other NDD patients – may offer some tentative support to the attraction account of CIB, as there is no clear evidence of visuospatial dysfunctions in the majority of the other NDD patients, however there is evidence of CIB in around 25% of other NDD patients, therefore CIB as a compensatory behaviour does not appear to be supported. Chapters 5 and 6 present further experiments, which address the concept of 'magnetic attraction' of behaviour towards the focus of attention.

Cancellation tasks are frequently applied as tests of visuospatial function and attention, and are commonly used in the assessment of neglect – generally conceptualised as a symptom of impaired visuospatial attention (Ferber & Karnath, 2001; Halligan, Cockburn & Wilson, 1991; Peru et al., 2017). The results of the present study demonstrated that patients with other NDDs did not differ significantly from age- and sex-matched controls in the visible condition, but made significantly greater errors of omission than controls in the invisible condition. Despite the sparse literature on the use of cancellation tasks outside of assessments of visual neglect, observing a significantly greater number of errors of omission on the invisible cancellation task may not be surprising given the reliance on spatial working memory for successful completion of the task (Stropford, Thompson, Neary, Richardson & Snowden, 2012). Further analysis of the cancellation task is presented in Chapter 5, Section 5.5.2; this provides a greater level of insight into the components of the task and the cognitive abilities into which these response behaviours provide insight. Section 4.4.4 within this chapter discusses the potential diagnostic utility of the cancellation task for distinguishing PCA patients from other NDD patients.

4.4.3 Rates of Impairment

The M-LAST and cancellation tasks yielded the highest rates of impairment values from the battery as a whole. The invisible cancellation task is a non-standard version of a traditional task, which is commonly used in the assessment of visuospatial and attentional disorders such as neglect. In addition, the line bisection task yielded promising rates of impairment values, based on control-generated cut-offs for normality. Further analysis of the gap bisection task, and its potential utility as a diagnostic tool for PCA are discussed in greater detail in Chapter 5. The use of alternative versions of the traditional tasks of line bisection and cancellation for identifying deficits associated with PCA potentially contradicts the status quo, and is discussed in further detail below. In addition the finding of a high rate of impairment value for PCA patients on the M-LAST task, a task not previously applied in the assessment of these patients, is another lead on what may be a valuable diagnostic tool. Further discussion on why these tasks may be promising diagnostic tests, and the implications this may have are discussed in detail in Section 4.4.4, below.

4.4.4 Line Bisection and Cancellation Tasks as Diagnostic Clinical Tools

The use of gap bisection, visible cancellation, and M-LAST tasks are diagnostically appealing as all are very quick to deliver, can be presented on a computer (provided that it has a touchscreen) therefore making results available to the clinician immediately after completion of the task, and would be inexpensive to use. Note that the M-LAST task has not, at the time of writing, been presented as a computerized task but with touchscreen technology and the use of a stylus this could theoretically be translated to a computerized version, which would further enhance the appeal of this task diagnostically. Task instructions for each would be readily translatable into other languages and there is, at the time of writing, evidence that systematic practice effects are not present for the cancellation task or bisection task (Wokciulik, Rorden,

Clarke, Husain & Driver, 2004; Butter & Kirsch, 1992), although to date no investigation into possible practice effects on the M-LAST has been conducted.

Paper-based cancellation and line bisection tasks have a long history of use to detect symptoms of neglect. Lateralised impairment on these tasks is associated with contralateral hemispherical impairment. Patients with PCA, for example, typically demonstrate left-sided neglect as a consequence of generally more severe right-sided occipitoparietal damage (Andrade et al., 2010; Nestor, Caine, Fryer, Clarke & Hodges, 2003; Whitwell et al., 2007). Spatially biased performance on cancellation tasks is a strong predictor of other symptoms of neglect, such as ignoring contralesionally located objects in space (Ferber & Karnath, 2001).

The finding that PCA patients were better distinguished from other NDD patients on the visible, but not the invisible, version of this task challenges the assertion that invisible cancellation tasks are more revealing of symptoms of neglect (Wojciulik, Rorden, Clarke, Husain & Driver, 2004). The additional observation that other NDD patients performed worse than age- and sex-matched controls on the invisible cancellation task (making significantly greater errors of omission) may be explained by processes other than deficits in visual attention as cancellation tasks may target a much broader scope of cognitive processes than visible cancellation. For example, in visible cancellation tasks it is logical that visuospatial and attentional systems are challenged. The individual must identify and touch each target in the display, requiring the ability to see the whole display (visuospatial awareness) and attend to each target (which, of course, requires attention). However, in invisible cancellation tasks there may be more cognitive systems implicated in order to perform successfully. For example, the individual must remember which targets they have touched already (visual working memory), and most likely should apply a systematic method of target selection in order to avoid misses, retouches or bounces (requiring executive control). Perhaps, therefore, the invisible cancellation task is disproportionately more difficult than visible cancellation to

the point where 'failures' are far more common (as observed by the fact that other NDD patients performed no differently from controls on the visible cancellation task but performed significantly worse than controls on the invisible cancellation task – PCA patients performed significantly worse than controls on both). For a task to be useful diagnostically, it should be titrated to the level of impairment. It would not be useful diagnostically, for example, to have a task that is so difficult that everyone fails it. Calculating disease-specific cut-offs for normal performance affords the task greater disease discriminatory properties. Additional analysis of the cancellation and line bisection tasks are discussed in further detail in Chapter 5, where further elaboration on the use of these tasks diagnostically and suggested cut-offs for impairment are proposed.

Recent evidence of a dissociation between the cancellation and line bisection tasks has led to cancellation tasks being favoured for diagnosis of neglect (Ferber & Karnath, 2001). There is evidence that the differential performance on these tasks may be a result of distinct encoding systems with cancellation tasks requiring an egocentric reference system used for allocation of visual attention, and line bisection tasks using an allocentric reference system focusing attention on external objects (Keller, Schindler, Kerkhoff, von Rosen & Golz, 2005).

The finding that PCA patients are impaired on both the cancellation and line bisection tasks may imply general deficits in both egocentric and allocentric attentional encoding. Patients with other NDDs were impaired on the invisible cancellation task when compared to controls, which may indicate a level of egocentric attentional encoding deficit. However, it seems likely that success on the invisible cancellation task implicates more than just an egocentric attentional encoding system, as discussed above.

At the group level, analysis on mean response position on the two conditions of the line bisection task did not reveal any statistically significant differences between PCA patients, other NDD patients or controls. Only around 20% of

other NDD patients presented as impaired on both the line and gap conditions. In contrast, the majority of PCA patients were impaired on the gap condition, which may be driven in part by simultanagnosia (leading the patients to be unable to perceive both endpoints). This task provides a further example of the need for tailored cut-offs for normal performance, since using cut-offs derived from healthy controls did not discriminate between patients well, as evidenced by the null results. Despite these results, PCA patients appeared to make greatly rightward errors. Other NDD patients performed in a manner reminiscent of 'exaggerated' controls.

The finding of a behavioural distinction between the line and gap bisection tasks has received some attention previously (Mashall & Halligan, 1994; Bisiach, Pizzamiglio, Nico & Antonucci, 1996; McIntosh, McClements, Dijkerman & Milner, 2004; Urbanski & Bartolomeo, 2008). The current consensus is that bisection errors observed in neglect patients on these tasks are a consequence of competition between right- and left-sided representations of the line (Urbanski & Bartolomeo, 2008; Bisiach et al., 1998). This has also been conceptualised as representational space being progressively 'relaxed' contralesionally and progressively 'compressed' ipsilesionally (Savazzi, Posteraro, Veronesi & Mancini, 2007). A number of studies have observed that bisection in gap conditions leads to reduced neglect bisection errors when compared to the line condition. One proposed explanation for the greater bisection symmetry observed in gap bisection rather than line bisection tasks is due to different spatial processes subserving the estimation of filled (line bisection) and unfilled (gap bisection) distances, with unfilled distances typically less impaired in neglect (McIntosh et al., 2004; Karnath & Ferber, 1999). The prevailing hypothesis, however, is that the reduction of neglect observed in gap bisection is the consequence of increased attentional cueing to both sides, as the task instructions require the participant to actively search for both endpoints, i.e. both dots (McIntosh et al. 2004; Bisiach et al. 1996; Urbanski & Bartolomeo, 2008). A more accurate calculation of the true midpoint would

therefore be possible as the individual would be giving more equal weighting to both endpoints.

Extrapolating further from the results of the present study it is possible that, for patients with PCA within this sample, the inherent attentional cueing to both end points provided in the gap condition did not benefit performance. PCA patients did not differ significantly on mean response position between the two conditions, therefore it is possible that either their left sided visual neglect was so extreme that the left sided gap is not effective as an attentional cue, or that there is an additional visuospatial, visuomotor or visuoattentional processing deficit which influences performance - such as simultanagnosia or optic ataxia.

4.4.5 Future Directions for Research

As with most small-scale clinical research projects, access to a sufficient number of patients in order to make more wide-reaching conclusions is often a limitation, and this was certainly the case within this study. Another caveat to the results discussed herein is the possibility of selection bias within this sample. All patients who responded to the initial letter of invitation were invited to take part in the study, therefore those who completed the study may not be a representative sample. There is evidence to suggest that departures from representativeness are magnified with increasing age (Golomb et al., 2012), therefore these results have been interpreted with caution.

A further methodological restriction to this study was the requirement to include abridged versions of many of the subtests. This resulted in a rather limited ability to make inferences on the early visual abilities of patients. However, this was unavoidable given the need to keep the time for completion of the screening testing within reasonable limits.

Nevertheless, the results of the present screening battery challenge some well-established views on which tests are most effective at detecting neglect, and

hence those which might be diagnostically useful for discriminating PCA from other NDDs, given the recently published guidelines which place space processing deficits as the most commonly observed symptom of PCA (Crutch et al., 2017). These early indications are highly speculative due to the limited patient sample – but the implications are strong enough that future research should be pursued to expand on these results with a greater array and diversity of patients. These results offer a contribution towards a better understanding of how best PCA may be identified in clinical settings, and specifically what tasks may be best applied to identify the characteristic impairments of PCA.

5. Experimental Chapter: Visual Attention

5.0 Introduction

5.0.1 Visual Attention

Visual attention is the process which "turns looking into seeing", the means by which the bombardment of visual information that the visual system receives on a moment-by-moment basis is parsed into relevant and actionable components (Carrasco, 2011, p.1484). Visual attention is the most widely studied perceptual system, most likely because it allows an understanding of how the 'attentional beam' is moved to various areas of the visual field, and how this beam is subsequently 'focused', changing the level of detail with which a certain area is processed (Raz, 2004). Many metaphors have been applied in the description of visual attention, but perhaps the most pertinent – based on current understandings – is the notion of an attentional 'spotlight' (Norman, 1968; Posner, 1980; Raz, 2004), acting somewhat like an attentional aperture which can be expanded to encompass a more global picture, or narrowed to provide fine-level detail. One conceptualisation of this is the difference between reading (wide attentional spotlight) and proofreading (narrowed attentional spotlight) (Raz, 2004).

A number of psychological models of attention have been proposed which characterise attention in different ways. Hasher and Zacks (1979) proposed that attention was critical for the encoding of memory and that differences in attentional capacity therefore result in differential performance on memory tasks requiring effortful processing (e.g. those that require more attentional capacity). Schneider and Shiffrin (1977) developed the idea of attention being a limited capacity system, proposing that automatic processing proceeds through activation of learned sequences, stored in long-term memory, requiring no attentional resources whereas controlled processing is capacity-limited and

requires attentional resources. Almost a decade later, Norman and Shallice (1986) suggested that the primary role of attention is in the control of action, and that most human action sequences can run without the need for deliberate attention, except in circumstances where the action is novel in some way, such as if the action is an alternative to a usual action, or if a habitual action is wilfully prevented from happening. In this model, the attention system therefore acts as a 'supervisor' to motor action (Norman & Shallice, 1986). Baddeley furthered the ideas proposed by Norman and Shallice, suggesting that the central executive of working memory acts as an 'overseer' which directs attention and coordinates the activities of the other components of the working memory system (such as the phonological loop and visuospatial scratchpad) (Baddeley, 1986; Morris & Jones, 1990).

Perhaps the model of attention most relevant to the research reported within the present chapter is the model proposed by Posner & Petersen (1990). Following a review of the anatomical literature, when neuroimaging was still in its infancy, the authors identified three discrete anatomical networks for attention, proposing that each was individually concerned with orienting, altering, and executive control (Posner & Petersen, 1990; Carrasco, 2011; Fernandez-Duque & Black, 2006). Posner and Petersen's original model proposed three additional characteristics of the attentional system (1990). Firstly, that the attentional system is anatomically separate from the 'data processing' systems which process sensory input, make decisions, and produce outputs, therefore attention interacts with other parts of the brain but maintains its own identify (Posner & Petersen, 1990; Petersen & Posner, 2012). Secondly, that the attention system is a network, not localised to one specific anatomical centre, nor a general brain function, but branching and accessing different brain regions (Posner & Petersen, 1990). Thirdly, that the areas implicated in attentional processing carry out different functions which can be described in functional cognitive terms (Posner & Petersen, 1990).

The framework proposed by Posner and Petersen is still operative today, having been refined in the intervening years with support from advances in neuroimaging and neuropharmacological techniques which in turn have led to a wealth of clinical data, providing evidence for the functional localisation of each branch of the proposed attentional network (1990; Petersen & Posner, 2012; Carrasco, 2011). The 'alerting' network, concerned with maintaining a state of receptiveness to incoming stimuli, is associated with the frontal and parietal right hemisphere (Marrocco & Davidson, 1998; Petersen & Posner, 2012). The second network is associated with attentional 'orienting', and involves selecting and prioritizing relevant information from sensory input (Carrasco, 2011). The 'orienting' network is associated with posterior regions including the superior parietal lobe, temporal parietal junction, and frontal eye fields (Corbetta, Kincade, Ollinger, McAvoy & Shulman, 2000; Petersen & Posner, 2012). Corbetta and colleagues demonstrated, through the application of event-related fMRI, that voluntary and involuntary orienting of attention are associated with the activation of distinct brain regions (Corbetta et al., 2000). Specifically, the intraparietal sulcus was active before target presentation during voluntary attentional orienting, whereas the right temporoparietal junction responded to target presentation more strongly when the target occurred at an unattended location, i.e during attentional re-orienting (Corbetta et al., 2000). The third network is the 'executive control' network and is concerned with decision-based attention, resolving conflicts among possible responses, and is associated with the anterior cingulate and lateral prefrontal cortex (Botvinick, Braver, Barch, Carter & Cohen, 2001).

Visual attention can be further categorized into three different subtypes: spatial attention, feature-based attention (FBA), and object-based attention (Carrasco, 2011). This allows for the optimisation of visual processing by the visual system, whereby spatial attention directs the viewer to a particular location in the visual space (either overtly, where eye movements to an object correspond with the focus of attention, or covertly, where attention is moved to a relevant location without corresponding eye movements). FBA guides the viewer to

particular features in the scene (e.g. colour, orientation, or motion), and object-based attention sees the structure of an object influence visual attention (Maunsell & Treue, 2006; Carrasco, 2011). Attention, or deficits thereof, can affect perception and behavioural performance by altering the subjective appearance of a stimulus or object (Carrasco, 2011).

5.0.2 Visual Attention in Neurodegenerative Disease

Historically, attention was seen as a general and non-specific factor affecting performance within dementia (Perry and Hodges, 1999). However, converging lines of evidence as well as the development of Posner and Petersen's model of attention have led to speculation that deficits seen in different presentations of dementia may be a consequence of deficits in parts of the attentional system (Posner & Petersen, 1990). For example, it has been speculated that issues with conducting activities of daily living, often observed at the earliest stages of AD, may be a consequence of attentional deficits, rather than a result of a purely amnesic syndrome as previously held (Perry & Hodges, 1999). As a consequence of the expansive research which has been conducted within the field of attention over the last twenty years, symptoms representing deficits of specific forms of visual attention have been identified, with associated neural correlates.

The identification of PCA as a distinct clinical syndrome, generally characterised as the 'visual variant' of AD, has additionally piqued the interest of visual attention researchers, and has led to further study into the manifestation of these specific symptoms within PCA patients and, to a lesser extent, the dementia population as a whole (Aresi & Giovagnoli, 2009). Indeed, the recently published formal classification framework for PCA, developed by Crutch and colleagues, identifies core cognitive features of PCA, many of which fall within the 'phylum' of visual attention (such as space perception deficits, simultanagnosia, object perception deficits, and optic ataxia) (Crutch et al., 2017). See Chapter 4 for further discussion on this framework.

Discussion on specific deficits of visual attention is presented below. This is framed with reference to the tasks and experiments used for their assessment, which are reported in this chapter. Predicted patterns of behaviour on each task, associated with specific visuoattentional symptoms, are additionally proposed.

5.0.3 Justification for Assessments of Visual Attention

The core visual attentional symptoms addressed by the assessments reported in this chapter include: optic ataxia, visual extinction, visual neglect, simultanagnosia, and endogenous orienting of visual attention.

Optic ataxia (OA) is a deficit in reaching to peripheral visual goals, usually occurring as a consequence of lesions to the posterior parietal cortex (PPC), specifically the superior parietal lobule (SPL) and areas around the intraparietal sulcus (IPS) (Andersen, Andersen, Hwang & Hauschild, 2014). OA, first described by Bálint in 1909 (followed by Holmes in 1918), was first characterised by Bálint as a visuomotor disconnection and then by Holmes as a global impairment in spatial perception, which he identified as 'visual disorientation'. OA, in the context of the dual stream theory of human visual processing, is used as the main evidence to attribute the 'how' function to the dorsal visual stream, as OA patients typically demonstrate deficits in accurately reaching to targets in the visual periphery as well as preshaping the hand appropriately for grasping (Goodale & Milner 1992; Milner & Goodale, 1995; Milner & Goodale, 2008; Rossetti, Pisella & Vighetto, 2003).

Converging lines of evidence have demonstrated that, rather than being purely a disorder of visually-guided action, deficits in attention are implicated in presentations of OA (see Chapter 9 for further elaboration) (McIntosh, Mulroue, Blangero, Pisella & Rossetti, 2011; Streimer et al., 2009). OA is usually evident following bilateral lesions, but can also follow unilateral lesions, manifesting as

misreaching within the contralesional visual field (the 'field effect'), or the contralesional hand (the 'hand effect') (Perenin & Vighetto, 1988; McIntosh, Mulroue, Blangero, Pisella & Rossetti, 2011). OA may manifest as misreaching to targets in the contralesional visual field, difficulty preshaping the hand for grasping, as well as an inability to correct reaches following initiation of the movement (Andersen et al., 2014).

OA often occurs in the context of Bálint's syndrome (when bilateral parietal damage is more severe), which forms a triad of symptoms; OA, simultanagnosia, and ocular apraxia (Andersen, Andersen, Hwang & Hauschild, 2014). So-called "pure" OA was described by Perenin and Vighetto in their seminal paper on the subject, where OA occurred in isolation (without any additional symptoms of Bálint's syndrome) following unilateral lesions largely restricted to the superior parietal lobe and intraparietal sulcus (Perenin & Vighetto, 1988; Striemer et al., 2009). Superimposition of the lesion profiles of a number of patients with 'pure' OA revealed a common region of convergence involving the IPS and SPL, which falls within the dorsal stream of visual processing, thus OA is considered a disorder of the dorsal stream (Karnath & Perenin, 2005; Rossetti, Pisella & Vighetto, 2003). The notion of 'pure' OA suggests that impairments observed are independent of perceptual or attentional deficits (which occur with ventral stream lesions) (Karnath & Perenin, 2005; Striemer et al., 2009; Milner & Goodale, 1995). There are no primary motor or sensory deficits associated with lesions to the SPL or IPS, therefore OA is most likely a deficit at a more integrative sensorimotor level (Andersen et al., 2014). More recent evidence has demonstrated that OA patients have deficits in attending within their ataxic visual field, which suggests that OA may not be entirely independent of attentional deficits (Striemer et al., 2009). Additionally, further research has been reported which suggests that OA may be driven by a proprioceptive, rather than purely visuospatial , deficit (Blangero et al., 2007). Further elaboration on this evidence is presented within the discussion section of this chapter.

OA is typically assessed as part of a neurological exam using the confrontation method, although there is a great deal of inconsistency in the reported behavioural measures used in the assessment of OA, both clinically and experimentally (Borchers, Müller. Synofzik & Himmelbach, 2013). The confrontation method involves asking the patient to grasp an object, for example, a pen, which is held in their peripheral vision (Vighetto, 1980). In addition to poorly reported methods, the vast majority of studies investigating OA patients specifically report the behaviour of only two patients, with few exceptions (Borchers et al., 2013; Perenin & Vighetto, 1988; Blangero et al., 2010). The present study assesses for the presence of OA using the confrontation method, which is the most widely used 'bedside' test of OA and has frequently been applied in the assessment of OA in patients with PCA (Borchers et al., 2013). An additional assessment for OA is reported in Chapter 6. Predicted patterns of behaviour on the OA by confrontation assessment would differ depending on whether the patient exhibited unilateral or bilateral OA. Bilateral OA patients demonstrate greater misreaching errors for eccentric targets, regardless of the hand used or the visual field of presentation (Dijkerman et al., 2006). Under confrontation, bilateral OA patients would be predicted to make some misreaching errors when reaching in central vision, with exacerbated errors when reaching peripherally. In unilateral OA, a hand or field effect is commonly observed, whereby reaching errors are exhibited only in the contralesional hand or field (Dijkerman et al., 2006; McIntosh, Mulroue, Blangero, Pisella & Rossetti, 2011; Perenin & Vighetto, 1988). Similarly, these misreaching errors would be predicted to worsen when reaching outside of central vision.

Visual extinction and visual neglect are well-documented neuropsychological consequences of right hemisphere damage, although there is some evidence that these symptoms may also be present following left hemisphere lesions (Smania et al., 1998). Visual neglect patients show a pathological lack of awareness of the contralesional visual field, whereas extinction patients fail to

detect contralesional stimuli only under simultaneous bilateral presentation (Smania et al., 1998).

Although there was some debate, historically, as to whether neglect and extinction were the consequence of sensory, attentional, or other factors, the present consensus is that neglect is not a unitary disorder but rather results from damage to several different cognitive processes (Halligan, Fink, Marshall & Vallar, 2003). Indeed, deficits in attention, intention, global versus local processing, spatial memory and mental representation may all contribute to a clinical picture of neglect. Therefore, neglect does not arise from disruption to a single overarching process (Halligan et al., 2003). Extinction is often taken as a cardinal sign indicating an attentional deficit among the various deficits of perception and exploratory behaviour which are associated with the neglect syndrome (Vuilleumier & Rafal, 2000). Extinction is associated with right-hemisphere damage, and often persists following recovery from a more severe neglect disorder (Vuilleumier & Rafal, 2000). Historically, the view has been that extinction and neglect share a common underlying mechanistic cause, whereby extinction and neglect share a qualitatively homogeneous continuum. However, case studies have demonstrated evidence of neglect but not extinction, as well as subtly different neurological correlates for the disorders (Cocchini, Cubelli, Della Sala & Beschin 1999; Kinsbourne, 1987; Vuilleumier & Rafal, 2000). Visual extinction was assessed in patients in the present sample using the confrontation technique (Cocchini, Cubelli, Della Sala & Beschin 1999). Patients exhibiting visual extinction would fail to identify movement from bilaterally presented stimuli on the contralesional side.

The multi-componential nature of neglect is well illustrated by performance on the two 'gold standard' tests of neglect: cancellation and line bisection (Milner & McIntosh, 2005). Most neglect patients will be identified by their performance on one or both of these tasks. However, double dissociations have occurred, which suggests that the two tasks cannot both be assessing the same unitary cognitive deficit (Milner & McIntosh, 2005). Although the characteristic

hallmark of visual neglect is the failure to attend to the contralesional hemispace, additional deficits which are not related to spatial bias have been observed in neglect patients; for example anosognosia for their impaired spatial processing, visuospatial working memory impairments, and reduced alertness and deficits in sustained attention (Bonato, 2012). These additional impairments may, in part, account for the differential performance occasionally observed on cancellation and bisection tasks. Visual neglect is generally characterised as a disorder of the ventral 'what' pathway, concerned with perceptual representations (Milner & Goodale, 1995; Milner & McIntosh, 2005). This assertion is based both on the typical presentation of neglect (whereby deficits manifest as deteriorated perceptual representations on one side of space), and also on the remarkable preservation of typically dorsal-stream mediated behaviour observed in neglect patients, although this preservation of functions is not without exception (Milner & McIntosh, 2005; Marotta, McKeeff & Behrmann, 2003).

Converging streams of evidence suggest that neglect can be characterised in general terms as a disorder of visuospatial attention (Ferber & Karnath, 2001; Halligan, Cockburn & Wilson, 1991; Peru et al., 2017; Kaplan et al., 1991). Indeed, recent evidence has demonstrated that increasing attentional demands can aggravate contralesional neglect on a cancellation task (Ricci et al., 2016). Bottom-up processes related to stimulus properties have been demonstrated to influence performance in cases of neglect (Ricci et al., 2016; Kaplan et al., 1991; Mennemeier, Morris & Heilman, 2004). Top-down factors have also been demonstrated to affect neglect performance, as well as factors not explicitly linked to the attentional domain (Ricci et al., 2016). One such example was a study in which a mathematical computation was required to identify targets in a cancellation task, which led to greater cancellation omissions relative to other task conditions, with all omissions occurring on the left side (Mennemeier, Morris & Heilman, 2004). Neglect patients' ability to process and subsequently act on information in 'neglected space' has been shown to be task dependent,

with recent evidence suggesting that right hemisphere lesions modulate task-related sustained attention (Kaplan et al., 1991; Ricci et al., 2016).

Left-sided visual neglect typically occurs as a consequence of right-hemisphere damage to the parieto-temporal junction. An interesting model which provides some explanation as to the modulatory effects of task requirements on performance, first posited by Kinsbourne in 1970, is based on hemispheric dominance, namely the 'opponent processor model' (Kinsbourne, 1970). Kinsbourne proposed that the two cerebral hemispheres are mutually inhibitory, therefore left-sided neglect following right-hemisphere damage is a consequence of the disinhibition of the left hemisphere's attentional vector towards the right side of space (Kinsbourne, 1970; Mennemeier, Morris & Heilman, 2004). The model further postulates that there is a more powerful rightward than leftward orienting tendency in neurologically normal individuals, therefore following contralateral brain damage these tendencies are highly magnified (Kinsbourne, 1987). In addition, there is evidence to suggest that the right hemisphere is dominant for attention, which offers some explanation as to why left-sided neglect is more commonly observed than right-sided neglect, and also why it is generally more severe in presentation (Heilman & Van Den Abell, 1980). Further elaboration on hemispheric dominance in neglect and the opponent processor model is presented in the discussion section of this chapter.

Visual neglect is assessed within this series of experiments using two well-established assessments. Namely, the line bisection and cancellation tasks (which are oft-cited tests of visual neglect), both of which were presented using a touchscreen rather than the traditional paper-and-pencil versions. No literature available at the time of writing reports the use of such computerized versions of these tasks in the assessment of patients with PCA. A novel 'gap' bisection condition is additionally presented, which was originally developed by McIntosh, McClements, Dijkerman & Milner, but has not been applied in the assessment of patients with any form of dementia prior to the present

investigation (2004). Presence of neglect on line bisection tasks is typically measured by the directional bisection error (reported in Chapter 4). However, alternative metrics for the measurement of attention and lateralised bias are presented within this chapter in order to assess their utility for identifying deficits associated with PCA (McIntosh, Shundler, Birchall & Milner, 2005). Similarly, number of target omissions is the most common measurement taken from cancellation tasks (presented in Chapter 4), but analysis of this task within this chapter presents alternative metrics which may be more sensitive and specific in the detection of symptoms of neglect. In addition, a pop-out and conjunction visual search task was created in order to screen patients for neglect, as well as to provide an overview of patient eye movement behaviour. Left-sided visual neglect on the visual search tasks would present as consistently missed targets within the left side of space. This task was additionally programmed with specific manipulations to the number of distractors which, while not constituting a test of simultanagnosia per se, allowed the opportunity to detect possible simultanagnosic symptoms, discussed further below.

Simultanagnosia is a deficit in the simultaneous perception of multiple objects and often results following damage to the SPL (Khan et al., 2015). As discussed in Chapter 4, there are a number of models of simultanagnosia and it remains disputed as to whether simultanagnosia is a deficit of object or of space perception, although it is generally agreed that it is an impairment of attention (Khan et al., 2015; Dalrymple, Barton & Kingstone, 2013). Simultanagnosic behaviour in the pop-out task would present as a nullification of the pop-out effect with increasing numbers of distractors. The requirement to engage a serial search strategy to identify the target in the pop-out condition would be as a consequence of the pathologically restricted attentional spotlight: adding more on-screen items (distractors) would mean the narrowed 'spotlight' would need to be moved around the screen to a much greater extent to identify the target and respond (Khan et al., 2016).

The pop-out and conjunction visual search tasks were also included in order to gain an overview of the eye movement characteristics of PCA (and non-PCA) patients within this sample. The tasks were conceived of and programmed for use in the present investigation. At the time of writing, no prior literature reports the use of pop-out or conjunction visual search tasks in the assessment of PCA patients. There are characteristic eye-movement features associated with presentations of PCA, namely; 'staircase' saccades (short and low amplitude saccades) and sticky fixation (or ocular apraxia, one of the triad of symptoms in Bálint's syndrome) which manifest as fixations of abnormally long duration, as well as redundant fixations (possibly a consequence of an impaired inhibition of return) (Shakespeare et al., 2015; Beh et al., 2015; Crutch, Yong & Shakespeare, 2016). One study examining the eye movement characteristics of PCA patients compared to typical AD and controls found 80% of PCA patients showed eye movement abnormalities, compared to 17% of typical AD patients and just 5% of controls (Shakespeare et al., 2015). Both PCA patients and typical AD patients demonstrated differences from controls on eye movements. Typical AD patients differed from controls mainly on characteristics of fixation and pursuit, whereas PCA patients differed on all of fixation, saccades and pursuit (Shakespeare et al., 2015).

A further behavioural correlate associated with simultanagnosia is that of impaired global form processing - an inability to see the 'forest' but not the 'trees' (Thomas, Kveraga, Huberle, Karnath & Bar, 2012). Neurologically normal participants typically show a global precedence, whereby the global properties of a scene are resolved first (Thomas et al., 2012). The Navon task is typically used to assess global and local form processing by means of figures in the form of a large letter (global form) made from repeated copies of a smaller letter (local form) (Navon, 1977). The global and local form can be congruent (where the large letter is the same as the smaller constituent letter forms), or incongruent (where the large letter is comprised of forms of a different letter) (Navon, 1977). In the Navon task, neurologically normal participants demonstrate interference effects, observed for the global but not the local form,

with faster reaction times observed for congruent global forms (Navon, 1977; Thomas et al., 2012). In contrast, individuals with simultanagnosia show a profound inability to integrate multiple visual elements from a scene, and thus do not show the global precedence effect – instead showing a local precedence effect as a consequence of their preserved ability to recognise individual or local elements (Thomas et al., 2012; Huberle & Karnath, 2006). The spatial distance between elements has been observed to modulate global form recognition in simultanagnosics, with a reduced intra-element distance improving global form recognition (Huberle & Karnath, 2006). Perhaps relatedly, PCA patients have been reported as having an inverse-size effect, whereby larger font sizes are harder to read than smaller (Yong et al., 2014). A striking example of such an effect was reported by one individual with PCA, who was unable to read the headlines of his newspaper but could easily read those of another passenger reading the same paper further down the train carriage in which he was travelling (Yong et al., 2014). This effect has been attributed to a reduction in the effective visual field in PCA, which may in turn relate to the narrowed attentional window hypothesis of simultanagnosia (Yong et al., 2014). A novel 'relief' condition was created and additionally tested as part of the Navon experiment reported within this chapter. The relief figure was comprised of a large (global) letter made of negative, unfilled space within a field of small letters (local). In other words, an absence of small letter forms in an otherwise filled field was what formed the shape of a large letter. This condition was included to establish whether the local can 'become global' for simultanagnosics, thus reversing the local precedence effect.

The Posner task is another task considered a 'gold standard' test, used in the assessment of deficits in spatial attention (Perry & Hodges, 1999; Hayward & Ristic, 2013; Losier & Klein, 2001). Specifically, the task reported within this chapter assessed endogenous (voluntary) rather than exogenous (reflexive) attentional control (Hayward & Ristic, 2013; Posner, 1980). Deficits in spatial attention (such as visual neglect) would be expected to result in errors on this task, whereby targets appearing in the neglected space are either missed, or

result in greater reaction time costs than targets in the unimpaired visual field. Posner and colleagues proposed a framework which describes changes in the direction of attention, where attention is first *disengaged* from fixation, and is then *moved* to the cued location and subsequently *engaged* at the cued location (Posner, Cohen & Rafal, 1982). When attention has been engaged at a congruent location (e.g. the cue directed attention to the real location), responses can be quickly initiated (Losier & Klein, 2001). However, when the cue and target location are incongruent, attention must be disengaged from the incorrect location and subsequently moved and re-engaged at the true target location – which incurs a cost in reaction time (Losier & Klein, 2001; Posner et al., 1982). Patients exhibiting visual neglect may demonstrate a 'disengage deficit', whereby RTs to validly cued targets in ipsilesional and contralesional sides of space are relatively comparable, but RTs to invalidly cued targets are much slower in the contralesional (neglected) half of space (Losier & Klein, 2001; Posner et al., 1982). A disengage deficit is therefore detected from an abnormally long response time to invalidly cued targets in the contralesional side of space (Losier & Klein, 2001). There is some evidence that PCA patients may experience poor attentional disengagement from the current focus of attention, likely as a consequence of slower oculomotor target identification, in turn resulting from weakened input from the parietal and occipital lobes (Shakespeare et al., 2015). Disengage deficits may therefore result from disruptions to visual attentional processing other than neglect.

5.0.4 Aims

The primary aim of the series of experiments and assessments reported within this chapter was to better characterise the visuoattentional deficits associated with PCA in a manner more detailed than prior investigations of these abilities in PCA. The secondary aim was to determine whether visuoattentional deficits are present in patients with diagnoses other than PCA.

5.1 Method

5.1.1 Ethical Approval

See Chapter 4, Section 4.1.1 for details.

5.1.2 Recruitment

Clinical recruitment was conducted according to the outline provided in Chapter 4, Section 4.1.2. All clinical participants who had completed Phase 1 testing (screening) were invited to participate in the Phase 2 lab-based experiments (Phase 2A and B), described both within this chapter and in Chapter 6. Figure 5.1, below, provides a visual overview of the flow of patients from Phase 1 to Phase 2A/B for reference.

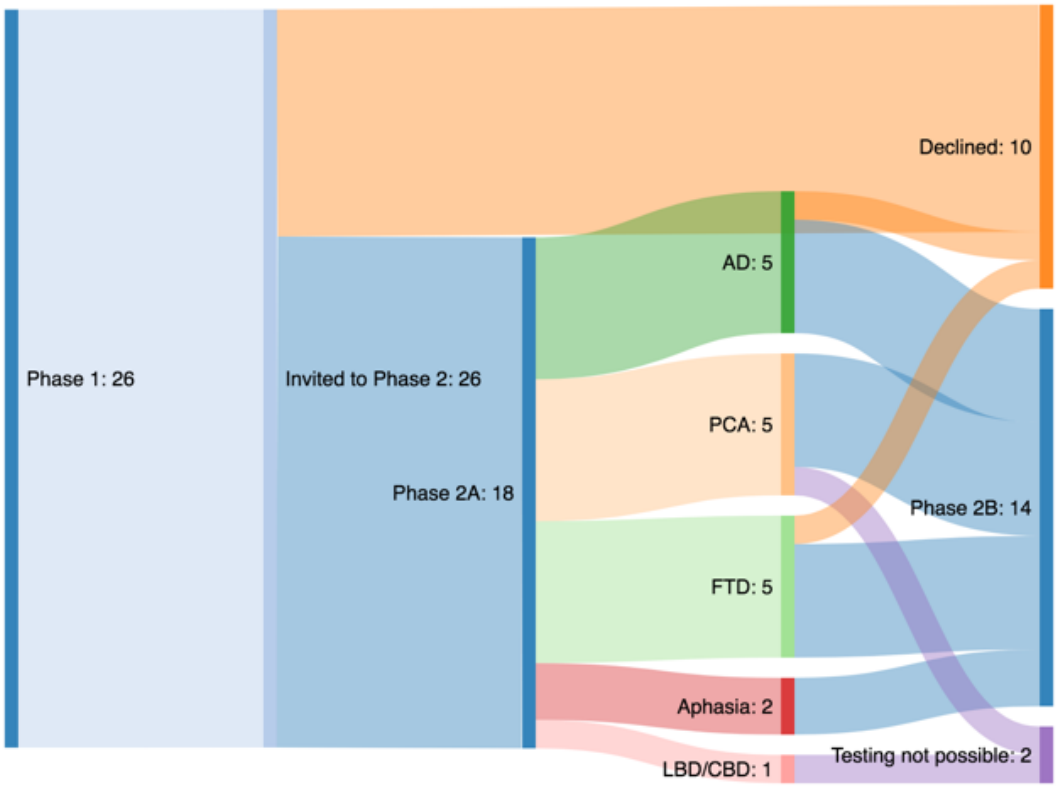


Figure 5.1: Diagram Illustrating Flow of Patients From Phase 1 to Phase 2A and Phase 2B Testing

5.1.3 Participants

5.1.3.1 Clinical

Table 5.1, below, presents a general overview of the characteristics of patients who attended the Phase 2 testing.

Diagnostic Group No.	Diagnostic Group Description	Number of Patients in Group	Mean Age at Date of Consent [range]	Gender	
				Female	Male
1	PCA	5	61.65 [52.01-70.09]	3	2
2	AD	5	63.84 [55.90 – 70.29]	2	3
3	FTD	5	63.11 [58.22 – 68.89]	2	3
4	Aphasia	2	67.73 [64.73-70.73]	2	0
5	LBD/CBD	1	78.41 [N/A]	1	0

Table 5.1: Demographic Characteristics of Patients in Phase 2

Chapter 4, Section 4.1.2, details the recruitment of clinical participants.

5.1.3.2 Control

Age- and sex-matched controls were recruited from the University of Edinburgh's Department of Psychology Volunteer Panel Database. They were contacted by email and invited to participate in a 3 hour long testing session, for which they were remunerated at a rate of £8 per hour. Controls were recruited to be age- and sex-matched to the 18 patients who attended the first lab testing session (Phase 2A), and would therefore match subsequent testing sessions completed by these same patients (Phase 2B).

Controls were 8 males and 10 females with a mean age at the time of testing of 65.43 (SD = 6.36) [range 53.67 – 79.13 years]. All control participants were self-reported as right handed.

5.2 Optic Ataxia & Extinction by Confrontation Assessments

5.2.1 Procedure, Materials & Measures

The informal assessment of optic ataxia by confrontation was conducted by asking participants to reach out and grasp a pen with their left and right hands in their left and right visual fields, under two conditions; free viewing and central fixation.

Participants were seated with the experimenter seated directly opposite them at a distance of approximately 80cm eye-to-eye. The experimenter then held a pen in either the upper left, upper right, lower left or lower right field of space (from the participant's point of view) and asked the participants to reach out and grasp the pen quickly, as if they were 'trying to snatch it away'. Participants completed this firstly under a look and grasp condition (saccade directly towards the object before grasping), and then under a no-look and grasp condition (maintaining fixation on the experimenter's nose). Participants completed each condition using their left and right hands separately. The assessments for optic ataxia and extinction were informed by the method described in Borchers, Müller, Synofzik & Himmelbach (2013).

The experimenter coded the grasping movements on a response sheet as detailed in Table 5.2, below.

Error Type	Description
Hit	Participant grasps pen in one fluid movement
Corrected error	Participant initially fails to grasp pen in first movement, touching the experimenter's arm or the pen in the first movement, but then successfully grasps the pen in a second corrective movement.
Uncorrected error	Participant does not grasp the pen in the first movement, reaching near the experimenter's arm or the pen initially, and then fails to grasp the pen in a second movement (possibly touching the experimenter's arm or the pen, but failing to grasp).
Miss	Participant neither grasps the pen in the first, nor any following movement, and the initial reach is not in the same visual quadrant as the pen.
Non-response	The participant fails to initiate any movement towards the pen, or fails to follow task instructions (e.g. does not maintain fixation under the fixation condition, or does not use the correct hand).

Table 5.2: Optic Ataxia by Confrontation Error Coding System

The informal assessment for extinction by confrontation was conducted with participants and the experimenter seated in the same manner as in the confrontation task. The experimenter held up their index fingers on an equal horizontal plane, palm towards the participant, at a distance of approximately 80cm apart, in each visual field. The experimenter then instructed the participants to indicate, by pointing, which finger they saw move. The participant was required to maintain fixation on the experimenter's nose. The experimenter would 'wiggle' the index finger of the target hand to generate the movement. A quick test was conducted initially to establish whether the participant was able to see unilateral movement from each index finger in turn. This established the salience of the movement required to elicit a response from the participant. The test then commenced with 9 unilateral left-sided movements, 9 unilateral right-sided movements, and 10 bilateral movements, presented in pseudorandom order. The experimenter noted the responses on a response sheet.

5.2.2 Analysis

Table 5.2, above, detailed the coding system for the optic ataxia by confrontation assessment.

Responses for the extinction by confrontation were recorded as either correct or incorrect for unilateral or bilateral trials. On bilateral trials where participants were incorrect, the side on which participants indicated that they saw movement was recorded.

5.2.3 Results

5.2.3.1 Optic Ataxia

Error percentage scores for each hand/visual field and condition are presented below. Non-PCA patients are presented in Figure 5.2, with PCA patients in Figure 5.3.

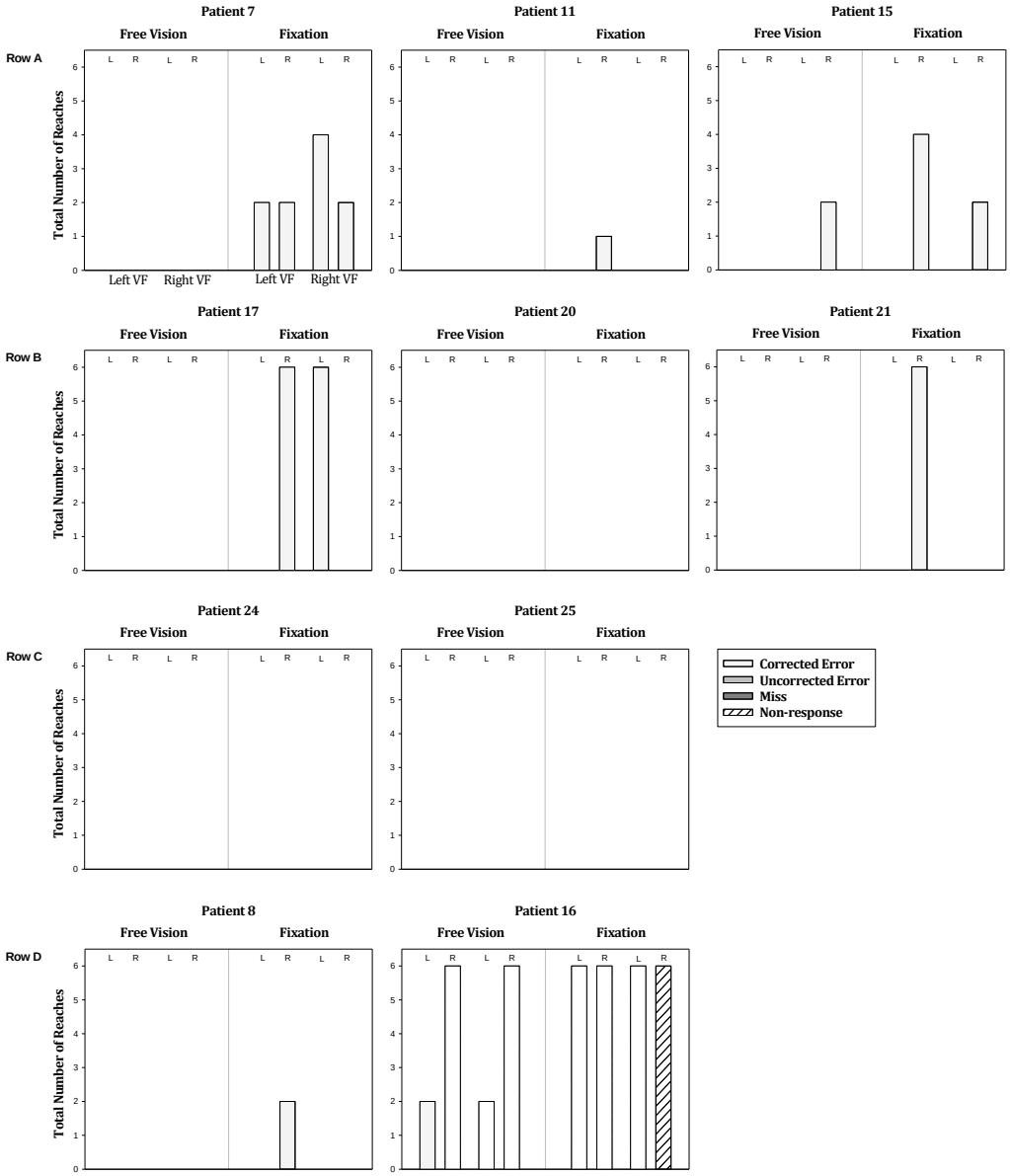


Figure 5.2: Non-PCA Patient Errors in Optic Ataxia by Confrontation
Note: No bar is equivalent to no error, i.e. a 'hit'. Superscripted 'L' and 'R' above columns refer to left and right hands. VF = visual field.
Rows A – C are other NDD patients, Row D are aphasia patients.

Initially, it can be observed that non-PCA patients generally made no errors in free vision, and usually only made errors in the central fixation condition. Those who made errors usually made corrected errors – therefore they were successful in grasping the pen after an initial misreach (see Table 5.2, above).

It is evident from Figure 5.2 that non-PCA patients perform almost perfectly (save for a few minor errors) in the free viewing condition. A greater frequency of errors is observed in the fixation condition – with 60% of non-PCA patients making at least one error (6/10). With the exception of patient 16, no hand or field effects were observed in the non-PCA patients. It can be concluded that these patients did not demonstrate optic ataxia-like deficits. Patient 16 represents an interesting exception to this rule (discussed below).

Patient 16 had a high frequency of non-response errors. In the free vision condition, this was due to this patient failing to use their right hand, and using their left hand only to respond. In the fixation condition, this patient was unable to maintain fixation. The patient continued to use only their left hand in this condition. Patient 16 presents an interesting case, where a non-PCA patient seems to exhibit possible PCA-like behavioural errors. This patient failed to use their right hand in any condition, and was unable to disengage their eye movements from their hand movement in the fixation condition – always looking at the target. This inability to decouple their movement from their locus of attention could be considered evidence of closing-in behaviour. This patient's spontaneous right-sided motor neglect under both conditions was all the more interesting given the fact that this patient was self-reported right handed. Note that this patient has a diagnosis of Aphasia.

Patient 17 made consistent corrected errors with the incongruent hand/visual field under fixation conditions. This pattern is not typical of OA, but does suggest some cost in the accuracy of performance for crossing the midline.

Figure 5.3, below, presents the PCA patient error data, where dramatically more errors can be seen in both conditions compared to non-PCA patients.

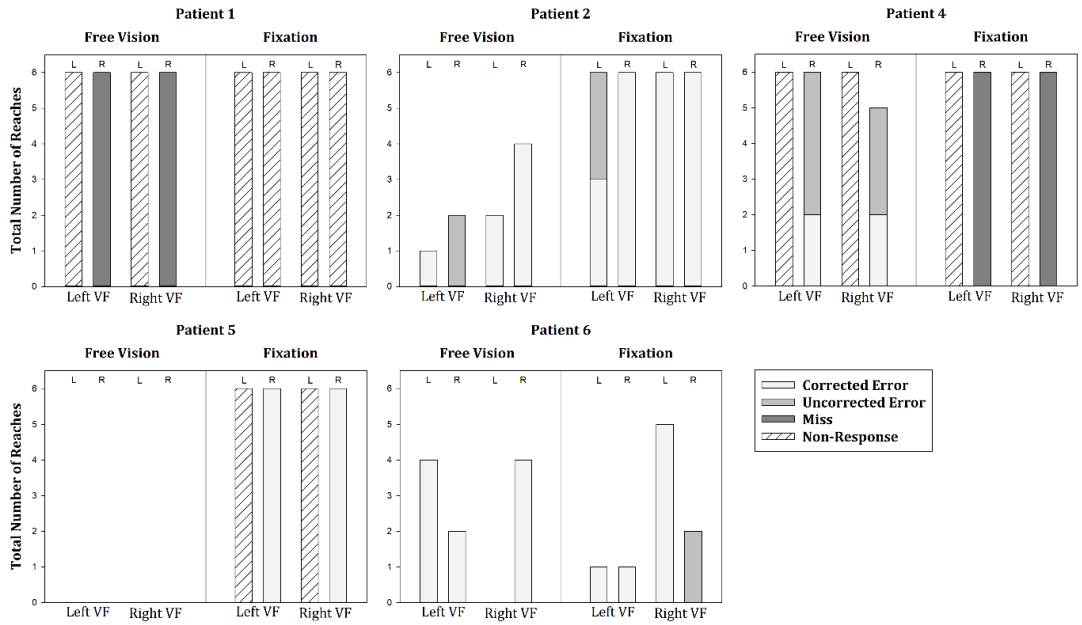


Figure 5.3: PCA Patient Errors in Optic Ataxia by Confrontation
Note: No bar is equivalent to no error, i.e. a 'hit'. Superscripted 'L' and 'R' above columns refer to Left and Right hands. VF = visual field.

Results from patient 1 were difficult to interpret as this patient exhibited left-sided motor neglect (defined operationally for the purpose of these investigations as spontaneous underuse of that hand). This motor neglect behaviour was observed in all other lab-based assessments which required the use of both hands. Therefore, this patient did not respond using their left hand in the free vision condition. Misreaching errors were observed for this patient with their right hand under free vision (misses). However, this patient failed to respond to any stimuli in the fixation condition, reporting: "there's nothing there". This patient commented further on their visual disturbances during the course of the extinction by confrontation testing, reporting: "I can't see [the experimenter's] fingers on either side, it's like holes. It's horrible because you think it's going to be there but it's not." The patient therefore 'progresses' from apparent left-motor neglect in the free vision condition, to an apparent inability to move either hand in the fixation condition - no attempts were made under fixation to reach to the targets. Such behaviour can be indicative of advanced OA. Previous investigations of OA in PCA have found similar results. Patient MTB, for example, failed to initiate movement towards peripheral targets in an

investigation of peripheral grasping, whilst maintaining the ability to initiate reaches for objects placed at their midline (Meek, Shelton & Marotta, 2013).

Patient 2 exhibits deficits in free vision, with left-handed performance appearing to worsen under fixation conditions. The right hand appears poor under both free vision and fixation conditions. These results suggest OA-like hand effects, whereby the OA is evident under both conditions for the right hand, and emerges under fixation for the left hand. Therefore this patient would likely meet the diagnosis for bilateral optic ataxia. This patient was observed to make wide, somewhat hesitant, sweeping arcs with either arm when reaching for the pen, with occasional jerky and stepped movements. These observations further support an observation of optic ataxia. More severe damage to this patient's left-hemisphere would be predicted from this observed pattern of performance.

Patient 4, as with patient 1, exhibits left motor neglect: failing to use their left hand under either free or fixation conditions. Therefore no data are recorded for this patient's left hand. This patient demonstrates deficits in reaching under free vision – but perhaps most striking are the results obtained from the fixation condition, where this patient responded not by grasping the pen, but by touching the experimenter's nose. This would be considered magnetic misreaching, as this individual failed to disambiguate where they were looking from where they responded. This magnetic misreaching behaviour is echoed in the gap bisection responses from this patient, presented in Section 5.4.3 of this chapter. Such striking misreaches may be considered a limb-dependent form of OA (Jackson, Newport, Mort & Husain, 2005).

Patient 5 performed perfectly under free viewing with either hand in either visual field. However, under fixation this patient presents with spontaneously induced left-sided motor neglect, failing to respond with their left hand. In addition, all right-handed responses under fixation were errors (corrected). The results from this patient therefore suggest that the task demands of reaching

under fixation are such that deficits in attention may be induced – in this case, manifesting as left-sided motor neglect. Alternatively, it is possible that pre-existing deficits in attention lead to misreaching behaviour under the increased attentional demands of the central fixation condition. These results are discussed in greater detail within the discussion section of this chapter, and may be an unusual presentation of OA.

Patient 6 appears the least impaired of the PCA patients, making generally fewer errors. Results from this patient are complex, and patterns of behaviour are challenging to extract. However, there appears to be some evidence of a congruent hand/field effect, with errors from the right hand worsening in the right visual field. This could be evidence of OA. However, errors from this hand are observed in both visual fields under both conditions, therefore it is possible that the progression from corrected errors to uncorrected errors between the free vision and fixation condition could be the result of other behavioural factors: there is not a convincing difference in misreaching errors between the two conditions. Likewise, it should be noted that between the free vision and fixation conditions, this patient grasps more targets successfully ('hits') with their right hand in the right visual field.

All PCA patients therefore demonstrated OA-like symptoms; misreaching errors under free vision, worsening under fixation, with motor neglect additionally reported in a number of patients. Notable, however, was the observation that motor neglect was a pattern elicited through task condition, with patient 5 spontaneously presenting with left-sided motor neglect under fixation. Overall, it is clear that this simple test for optic ataxia appears to be highly sensitive and specific for PCA – with very few errors (and particularly no errors 'worse' than a corrected grasp) from non-PCA patients, with one exception (patient 16).

5.2.3.2 Extinction

As with the assessment of optic ataxia by confrontation, the assessment of extinction by confrontation was sensitive and specific to deficits associated with PCA, with no non-PCA patients making any errors.

PCA patient 1 and patient 4 failed to respond on the majority of trials, with patient 1 reporting that they could not see the majority of trials as their vision had "holes". Patient 4 was untestable on this examination, as they failed to see any unilateral stimuli, even with increasing movement salience. This examination may therefore be too difficult for more advanced presentations of PCA. However, it may be useful to determine differential deficits between non-PCA and PCA in the earlier stages. Notably, the two patients who were unable to complete the task additionally exhibited left-motor neglect.

Figure 5.4, below, presents PCA patient accuracy data and response lateralisation data from incorrect bilateral trials. Patients 2 and 5 demonstrated very poor accuracy for bilateral trials, and variable accuracy for unilateral trials, with patient 2 demonstrating greater accuracy for unilateral right-sided stimuli, and patient 5 demonstrating the opposite pattern – with greater accuracy for unilateral left-sided stimuli.

On incorrect bilateral trials, both patient 2 and patient 5 exhibited some signs of left-sided extinction (particularly evident in patient 5). Given that patient 5 had good accuracy for unilateral left-sided stimulation, it can be concluded that the lack of responses to left-sided stimuli under bilateral stimulation is a consequence of extinction. Patient 2 shows a similar, although less dramatic, pattern of behaviour. Responses from patient 2 on incorrect bilateral trials are more suggestive of simultanagnosia, as errors do not indicate a bias towards either side of space as would be anticipated in neglect.

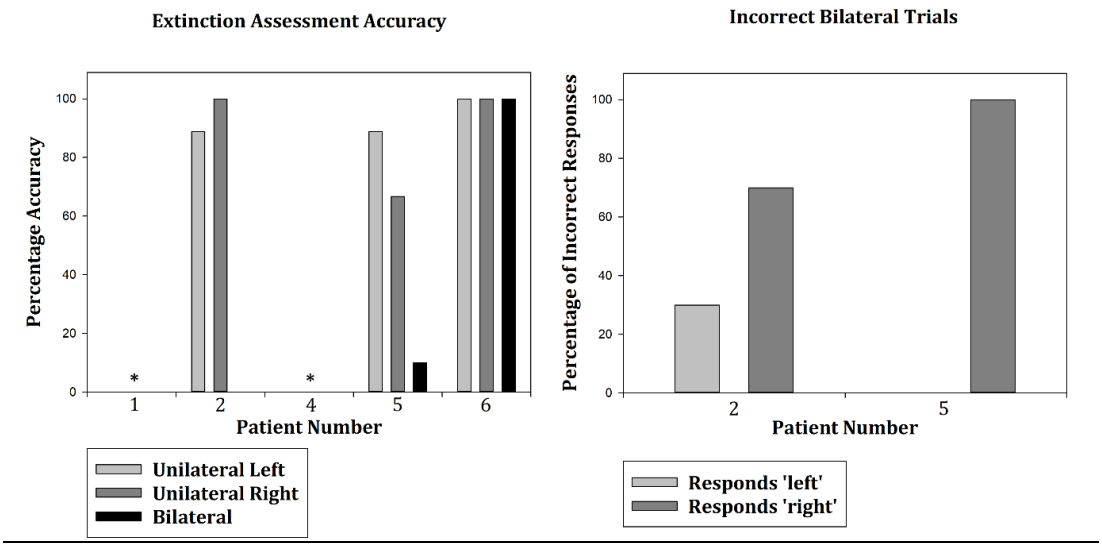


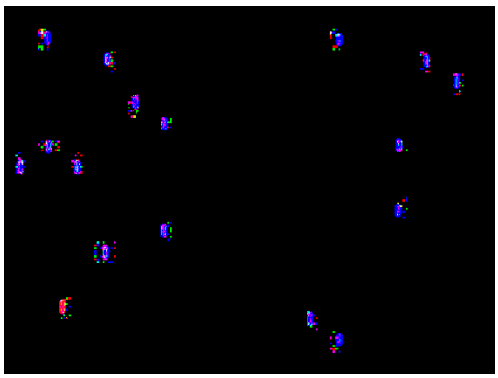
Figure 5.4: PCA Patient Extinction Results
Key: * indicates that no data were available for analysis due to patient non-response.

Patient 6 demonstrated perfect accuracy for all trials. What can therefore be observed from this extinction by confrontation testing is a spectrum of deficit: from visual impairment that is so great that meaningful interaction with the task was not possible (patient 1 and 4) to perfect accuracy on the other side of the spectrum (patient 6), with simultanagnosia (patient 2) and very striking visual extinction for left-sided stimuli (patient 5) observed 'in-between'. The results from patient 2 could be interpreted as being due to weakened peripheral vision. However, this patient was demonstrably able to detect peripheral stimuli under central fixation in the optic ataxia by confrontation task, therefore the results of the present task are more readily explained by simultanagnosia.

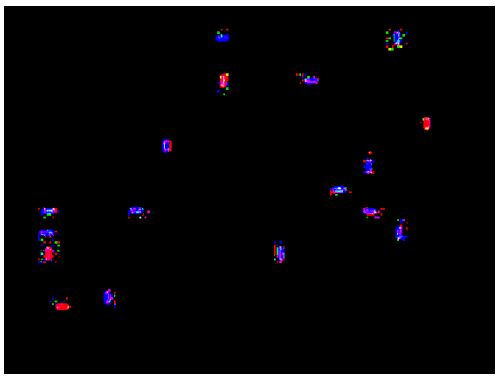
5.3 Pop-out and Conjunction Experiments

5.3.1 Procedure, Materials & Measures

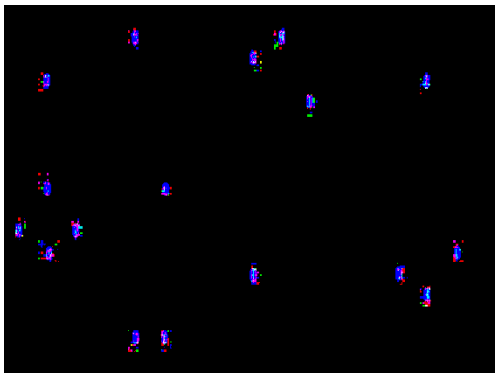
The pop-out and conjunction experiments were simple serial and conjunction visual search tasks, respectively, conducted in a lab using an eyetracker to record eye movements and a response pad to record response times.



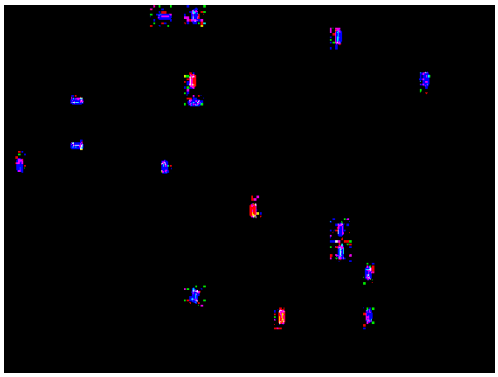
A. Pop-out experiment: target present (at location 2)



B. Conjunction experiment: target present (at location 2)



C. Pop-out experiment: target absent



D. Conjunction experiment: target absent

Figure 5.5: Pop-out/Conjunction Experiment: Example Stimuli with Target Present (A, B) and Target Absent (C, D).

The target in the pop-out task was an upright red bar (5 x 30 pixels). The background was black, and distractors were upright blue bars with the same dimensions. In the conjunction experiment the target was a horizontal red bar (30 x 5 pixels), presented on a black background. Distractors in the conjunction experiment were upright red and upright/horizontal blue bars of the same dimensions, with an approximately even proportion of red or blue distractors for each distractor count condition. Example stimuli from both the pop-out and conjunction experiments are provided in Figure 5.5. The tasks were custom programmed using Experiment Builder (Version 1.10.165).

Both the pop-out and conjunction experiments had targets appearing at the same 12 locations in visual space with 3 target eccentricities in the upper and lower quadrants on the left and right side of space. Targets were located at

retinal eccentricities of 2°, 6° and 10°. Figure 5.6, below, presents the target locations for both tasks.

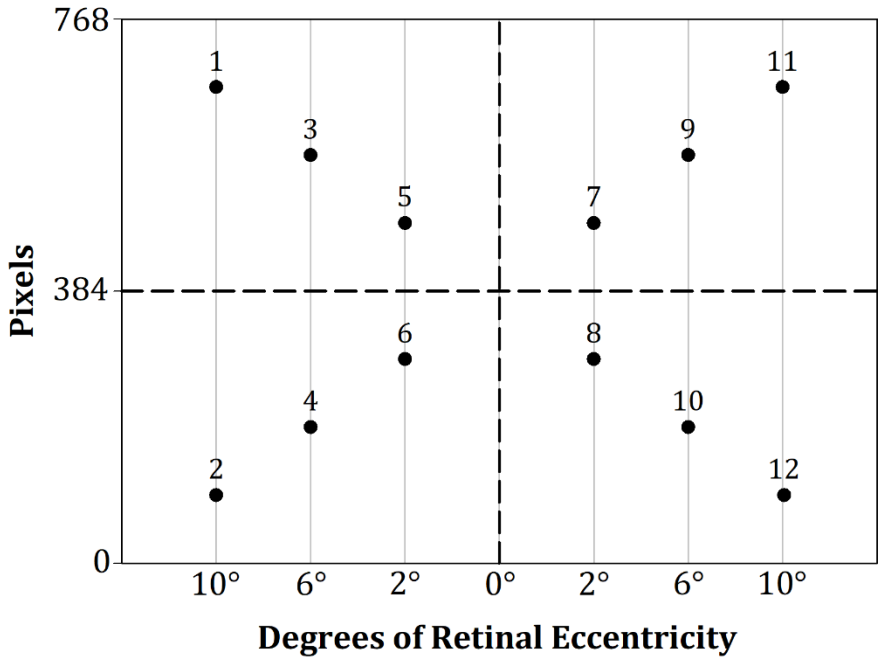


Figure 5.6: Target Locations
• Represents target location with location number code.

There were 6 distractor conditions, each corresponding to a different number of on-screen distractors (0, 1, 2, 4, 8, and 16 distractors), which resulted in 72 target-present stimuli images for each experiment (6 distractor conditions, with 12 different target locations), and 36 target-absent 'catch' trials, consisting of iterations of 1, 2, 3, 5, 9, and 17 distractors (6 distractor conditions, with 6 stimuli per condition). Therefore for each condition there were a total of 108 experimental trials. Using a random number generator to select stimuli, 10 of the stimuli from each condition were presented at the beginning of the assessment, which served as practice trials, but which were removed from further analysis. The stimuli were presented in random order for each participant across each condition.

Prior to commencing the experiment, participants were given the task instructions and shown 4 example images in order to establish whether they could reliably see the target in the display under task conditions. In addition, this pre-experiment instruction allowed participants to practice the response buttons to use in the experiment. Participants were instructed to respond using a hand-held response pad - the right hand pressing the right-sided button if the target was present, and the left hand pressing the left-sided button if the target was absent. Participants therefore held the response pad in both hands with their index fingers on the two buttons for rapid response. If no key was pressed, the program timed out automatically after five seconds and advanced to the drift correction screen.

The eyetracker camera focus was manually adjusted by the experimenter for each participant. Calibration was also manually conducted and validated across 9 points (or 5 points for participants whose eyelid physiology made 9-point calibration impossible). Between each stimulus, participants were instructed to fixate on a drift-correction circle in the centre of the screen, and the experimenter manually accepted the drift correction to advance to the next trial.

The images were generated with a resolution of 1024 x 768 pixels, and were presented on a monitor with the same resolution and a refresh rate of 60Hz. The monitor used was a Professional Series P225f monitor with an active display area of 386mm x 296mm. The monitor was secured at a viewing distance of 57cm, maintained through the use of a desk-mounted head and chin rest. The eyetracker was a desk-mounted Eyelink 1000. Recording was taken monocularly from the right eye for all participants.

After the practice block of 10 trials, there were a total of 6 blocks in the experiment with 18 trials in each. Between each block a white screen with the word 'INTERVAL' appeared, at which point the experimenter would ask the participants if they wanted to continue, or whether they would like to take a

break. Using a white background for the interval screen was also intended to prevent neuronal fatigue.

5.3.2 Analysis

Control data were used in order to characterise 'normal' performance for each task. These results were then used in order to generate cut-offs for normal performance (see Chapter 4, Section 4.2.1 for a detailed description of cut-off score generation).

A single-case 'slope-comparison' method was applied in order to quantify patient performance on each of the task conditions to the slope of the regression line produced for controls (Crawford & Garthwaite, 2004).

The method described by Crawford & Garthwaite states that summary statistics, rather than raw scores, should be used for the comparison of regression slope coefficients (2004). The use of summary statistics in this way has a number of practical benefits, the first of which is that the effect of violations of normality can be mitigated by using the median score for a given dependent variable. The pop-out and conjunction visual search tasks have not been applied previously to the assessment of PCA patients, therefore application of this method may provide some benefit to future research which may refer to these results. An additional benefit to applying the slope-comparison method (rather than the alternative method of *z* scores) is that the Type I error rate is not at risk of being inflated as it can be when using *z* scores to compare neuropsychological patients to healthy controls (Crawford & Garthwaite, 2004). In addition, quantifying performance using a slope also allows for comparisons to be made between patients and controls on estimated variances (Crawford & Garthwaite, 2004).

An initial data cleaning exercise was carried out prior to data analysis, in which the following exclusion rules were applied:

Dependent Variable	Exclusion Rule	Justification	No. of cases excluded (% of total trials)
Mean saccadic amplitude (meanAMP)	meanAMP >100, then eye movement data for that trial are excluded, behavioural data are retained	Visual inspection of meanAMP histograms revealed a cluster of responses which had theoretically impossibly large values. An upper cut off of 100 was applied to ensure that all true meanAMP values were retained.	106 (1.61%)
Reaction time (RT)	RT < 250ms, then both eye movement and behavioural data for that trial are excluded.	Visual inspection of the histograms revealed a clear bimodality with a local minimum of 250ms. RTs of <250ms were coded as anticipatory responses and were excluded.	710 (10.81%)
Blink duration (BD)	BD > 12% of total trial time, then eye movement data for that trial are excluded, behavioural data are retained	95% of trials had trial blink time percentages of less than 12%, therefore applying this rule captures the majority of trial data whilst excluding those trials for which there was excessive blinking which will have interfered with the eye movement recording.	318 (4.84%)
Button presses (BP)	BP > 1, then both eye movement and behavioural data for that trial are excluded	Multiple button presses imply that for that trial the task was not being correctly completed.	94 (1.43%)
All Eye Movement Data	If meanAMP and mean fixation duration cells are blank for conjunction task trials, eye movement data for this trial are excluded	Data are excluded on the basis that, in the absence of recorded meanAMP and mean fixation duration data, meaningful eye movement data have not been recorded for this trial. This does not apply to pop-out trials, where no recorded eye movements may be possible due to the pop-out effect of the target.	309 (4.71%)

Table 5.3: Pop-out & Conjunction Task: Data Cleaning Exclusion Criteria

Visual inspection of histograms for each dependent variable demonstrated that data were not normally distributed and subject to skew to differing degrees of severity. In order to address this issue of non-normality, median scores were calculated per participant for each dependent variable across the three within-subjects conditions, noted below.

- Condition (2 levels: pop-out and conjunction)
- Distractors (6 levels: 0, 1, 2, 4, 8, and 16 distractors)
- Eccentricity (3 levels: 2°, 6° and 10° of retinal eccentricity)

One exception to this was the dependent variable of mean *x* co-ordinate, for which a mean value, rather than median, was calculated. The mean was calculated for this variable, rather than the median, as it provided a more accurate overview of the true mean *x* co-ordinate, as many participants did not make many saccades during the pop-out task and hence a median value would not capture the true midpoint of the behaviour as accurately.

In order to limit the risk of Type I errors as a consequence of multiple comparisons, a more stringent alpha criterion of 0.005 was applied when interpreting the results of individual linear regression analyses. Instances when this criterion was applied are indicated within the text.

5.3.3 Results

5.3.3.1 Pop-out Task

Initial exploratory analysis to determine control performance on the pop-out task was conducted using a Repeated Measures ANOVA.

An initial group level analysis was conducted on control performance for target present trials. Controls demonstrated very few eye movements in the pop-out task, with no saccades on 36.7% of trials (range = 0-6 saccades). This is

consistent with the qualitative observation that most control participants kept their eyes fixated on the central point following the presentation of the drift correction cross, and made a rapid response on presentation of the trial image. Number of saccades was unaffected by both distractor condition, $F(5, 12) = 1.278$, $p = 0.335$, and target eccentricity, $F(5, 12) = 0.730$, $p = 0.498$. Following this group level analysis, individual regression analyses were conducted on median number of saccades by distractor number for each control participant. This regression analysis was non-significant in every case, using the more stringent alpha criterion of 0.005. The maximum estimated slope observed for controls was $\beta = 0.095$, in which instance 1.520 additional saccades would be made at 16 distractors (therefore, indicating very little effect of distractor number on number of saccades). The slopes of the control regression functions taken together were therefore flat.

A further group level linear regression was performed on patient data from this task in order to formally test the effect of both conditions on patient performance. In a similar manner to control performance, the results demonstrated that median number of saccades was unaffected by both distractor condition, $F(5, 8) = 0.583$, $p = 0.713$, and target eccentricity, $F(5, 8) = 1.152$, $p = 0.351$ for patients on the pop out task.

Patient No.	Group Code	Performance	
		Normal	Abnormal
1	1	•	
2	1		•
5	1		•
6	1	•	
7	2	•	
9	2	•	
11	2	•	
15	2	•	
17	2	•	
18	2		•
20	2	•	
24	2	•	
25	2	•	
8	5	•	
16	5		•

Table 5.4: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally (in median number of saccades made) on the Pop-out Visual Search Task

Key: Group 1 = PCA, Group 2 = Other NDD, Group 5 = Aphasia.

Note: 'normal', below the upper cut-off for healthy control performance. 'abnormal', above the upper cut-off for healthy control performance,

Table 5.4 presents individual patient performance coded as normal or abnormal in relation to the upper cut-off for normal performance, calculated from healthy controls (3.088 saccades). This was computed using the individual's overall median number of saccades in the pop-out condition (collapsed across number of distractors and target eccentricity). This table indicates that 76.92% of individuals (10/13) performed normally on this task, with two individuals from the PCA group and one individual from the other NDD group performing abnormally. Note that results from patient 16 are not discussed further, as Figure 5.8 demonstrates that this patient did not interact with the task in a meaningful way, therefore the results cannot be interpreted. Figure 5.7, below, presents the saccadic behaviour from the three abnormal patients.

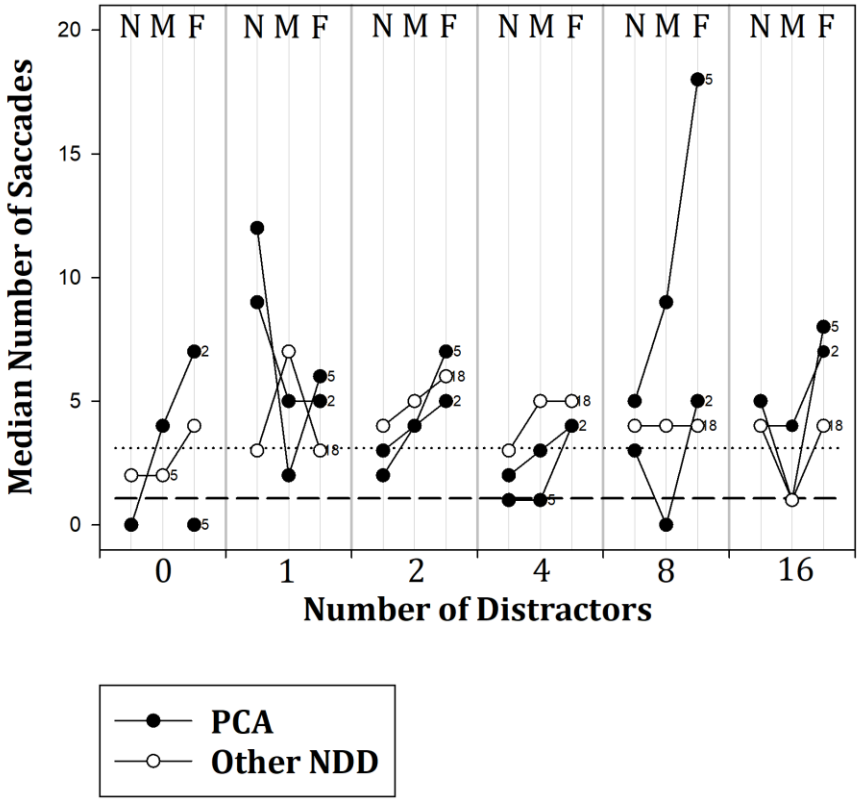


Figure 5.7: Line and Scatterplot Illustrating Median Number of Saccades for Patients (Abnormal Performance) Across Each Distractor and Target Eccentricity Condition
Key: — — — represents control mean, · · · · · represents cut off for normal performance
N = near eccentricity (2°), M = mid eccentricity (6°), F = far eccentricity (10°).
Superscripted labels refer to patient number.

Caution must be exercised when interpreting these data given that they are subject to noise due to a limited number of repetitions of each level of each condition. However, qualitatively it appears that the PCA patients were more affected by target eccentricity than the other NDD patient. Interestingly, distractor number appears to have little effect on the abnormally-performing PCA patients. This is surprising as PCA patients often show simultanagnosia, which would predict a greater number of saccades for increasing number of distractors. There are, logically, two reasons why a patient may make an abnormally large number of saccades. The first, which would be explained by a symptom such as simultanagnosia, is that patients are unable to see the target due to a pathologically restricted field of visual attention, therefore more saccades are required to locate the target. A second explanation would be that

patients are not applying top-down control strategies (as controls did, whereby they generally fixated at screen centre) in order to complete the task, which may be explained by executive dysfunction.

In order to assess whether a distractor effect was present for any individual patient, individual linear regression analyses were run, using the more stringent alpha criterion of 0.005, which was applied in order to limit the risk of Type I error.

The regression equation significantly predicted distractor number from median number of saccades for one individual (patient 11), $F(1, 4) = 68.333$, $p = 0.001$. However, closer scrutiny of the value of the regression slope for this individual ($\beta = -0.048$) demonstrates that even for the highest number of distractors (16), this individual will make approximately 1 additional saccade ($\beta * 16 = 0.768$ saccades). Therefore, although statistically there is a dependent relationship between median number of saccades made and distractor condition, the value is so small that it becomes behaviourally irrelevant.

The final analysis conducted on the pop-out task was on percentage accuracy. Cut-offs were calculated both for abnormality when compared to control performance and also for chance. These results are presented in Figure 5.8, below.

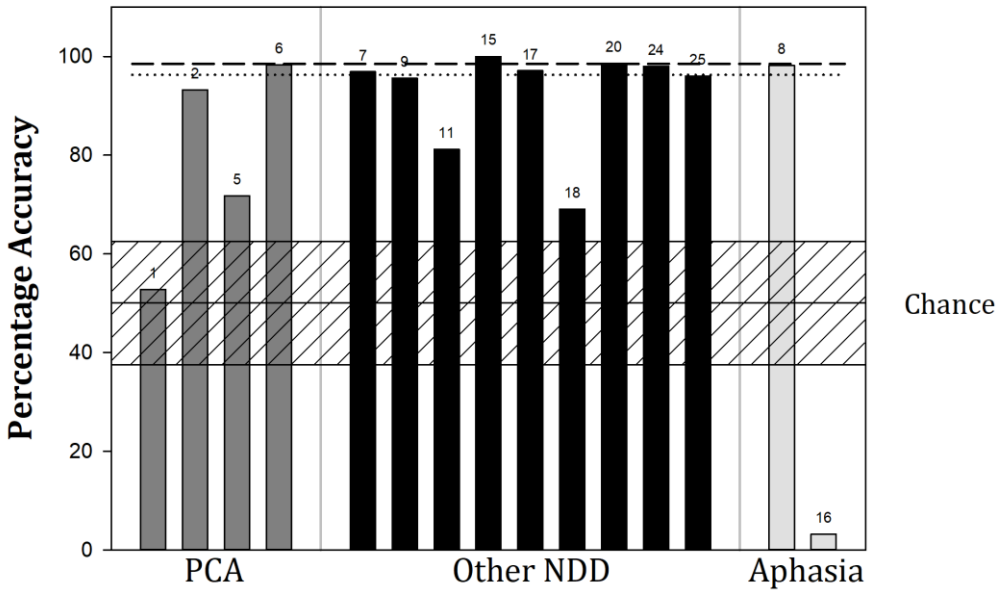


Figure 5.8: Bar Chart of Percentage Accuracy for Target Present Trials on Pop-out Condition
Key: — — — represents control mean, · · · · · represents lowest cut off for normal performance, shaded area within black lines represents upper and lower cut-off for performance at chance level.
Superscripted labels refer to patient number.
Note: Results for patient 25 are taken from a different response button, as this patient responded with the opposite button. Patient 16 did not respond on 96.8% of trials.

From Figure 5.8 it is clear that patient 1 was unable to interact with the task successfully, performing within the limits of chance. These results are not adequately explained by the presence of left motor neglect in this patient (which was observed in all other lab-based assessments). This patient was therefore not able to respond with their 'target absent' left-sided button (and never pressed this button) – but should have been capable of responding to target-present trials with their right hand. The abnormal correlation between the median number of saccades and number of distractors is therefore likely due to the fact that this individual was not performing the task correctly (see Table 5.4, above). Patient 7 presents an interesting case whereby the patient demonstrates almost perfect accuracy on the task, and yet has an abnormal saccade to distractor condition correlation. This patient may be approaching the task with a different task set than other patients and controls, which may be the

cause of the abnormal correlation value observed for this individual. Patient 16 did not interact with the task at all, failing to respond on 96.8% of trials.

This insensitivity to distractor number, evidenced by the finding that number of saccades was unaffected by the number of distractors presented, suggests that the patients experienced the pop-out effects of the target. The narrowed attentional window hypothesis for simultanagnosia would explain these effects, as the slope function for patients 2 and 18 were flat (like controls) but raised – thus, these patients applied a serial search in order to locate the target (which is behaviour that is expected on a conjunction search task), but once their attentional window included the target, the pop-out effect was present. Patient 2 was additionally observed to exhibit simultanagnosia on the extinction by confrontation task (Section 5.2.3.2, above), adding further support to this hypothesis.

In contrast, an object-based account of simultanagnosia would have predicted the same intercept as controls, but a steep slope whereby increasing number of distractors would require many saccades to locate the target. This would be anticipated because at zero distractors (the intercept) there would only be one item on-screen (the target), which would not induce the effects of object-based simultanagnosia, whereas any number of on-screen items greater than one would incur a cost in terms of the number of saccades required to find the target, inflated as a consequence of simultanagnosia. The regression slope produced by the results from patient 5 appears to follow this pattern of behaviour, although given that there was no statistically significant effect of distractor number of median number of saccades, caution should be exercised in interpreting any difference in behaviour here.

5.3.3.2 Conjunction Task

As with the pop-out task, initial group level exploratory analyses were performed in order to determine control performance on target present trials on the conjunction task, using a multiple regression. The dependent variables of interest were median number of saccades, mean saccadic amplitude, reaction time, and percentage accuracy.

A stringent alpha criterion of 0.005 was applied to these analyses. The results of the multiple regression analyses found that median number of saccades was predicted by both number of distractors and target eccentricity, $F(2, 246) = 82.899$, $p = 0.000$, $R^2 = 0.403$, with both independent variables contributing statistically significantly to the prediction ($p = 0.000$ for both number of distractors and target eccentricity). Likewise, median of mean saccadic amplitude was predicted by both independent variables, $F(2, 246) = 75.470$, $p = 0.000$, $R^2 = 0.380$, with only target eccentricity contributing statistically significantly to the model ($p = 0.000$, note that distractor condition was not significant, $p = 0.013$). Percentage correct was also predicted significantly by the independent variables, although these variables explained very little of the variance within the score – a reflection of the ceiling effect of performance for controls on this task, $F(2, 285) = 8.828$, $p = 0.000$, $R^2 = 0.058$; both independent variables contributed significantly to the model ($p = 0.003$ for both). Finally, reaction time was predicted significantly by the independent variables, $F(2, 282) = 102.351$, $p = 0.000$, $R^2 = 0.421$, and both independent variables contributed significantly to the model for this dependent variable ($p = 0.000$ for both).

Linear regression analyses were conducted for each individual in order to produce a slope and standard error value for the dependent variables of number of saccades, RT, and percentage accuracy using distractor number and eccentricity as the independent variables. Simple linear regression analyses

were conducted for mean saccadic amplitude using only target eccentricity as the independent variable.

Slope comparison analyses were subsequently conducted and are reported below. Following the method specified by Crawford & Garthwaite, slope coefficients were produced for each control participant (2004). These control slope coefficients were subsequently compared to individual patient slope coefficients using the companion program, published online by the authors ('SINGSLOPE.exe', Crawford & Garthwaite, 2004). This allowed for a comparison to be made between individual patients and the control group on whether that patient's slope differed significantly from controls, and to produce a point estimate of any difference.

In order to utilise the Crawford & Garthwaite slope comparison method, Bartlett's test for sphericity should be non-significant, as this indicates that the error variances of control slopes can be treated as equivalent (2004). Barlett's test for sphericity was not significant for variances in the following cases;

- Median number of saccades: distractor condition, X^2 (14) = 10.44, p = 0.729, and eccentricity condition, X^2 (14) = 1.89, p = 0.999.
- Reaction time: distractor condition, X^2 (14) = 20.42, p = 0.117, and eccentricity condition, X^2 (14) = 4.07, p = 0.995.
- Percentage correct: eccentricity condition, X^2 (9) = 3.41, p = 0.946.

Slope comparison analysis was therefore possible for these dependent variables under the specified conditions.

Barlett's test for sphericity was significant for variances in the following cases;

- Mean saccadic amplitude: eccentricity condition, X^2 (14) = 27.27, p = 0.017.
- Percentage correct: distractor condition, X^2 (9) = 19.51, p = 0.021.

In these cases where slope comparison was not possible, z-scores are plotted in order to allow for qualitative interpretation of any emergent patterns.

Results of these analyses are presented below grouped by condition (target eccentricity and number of distractors) (Figure 5.9).

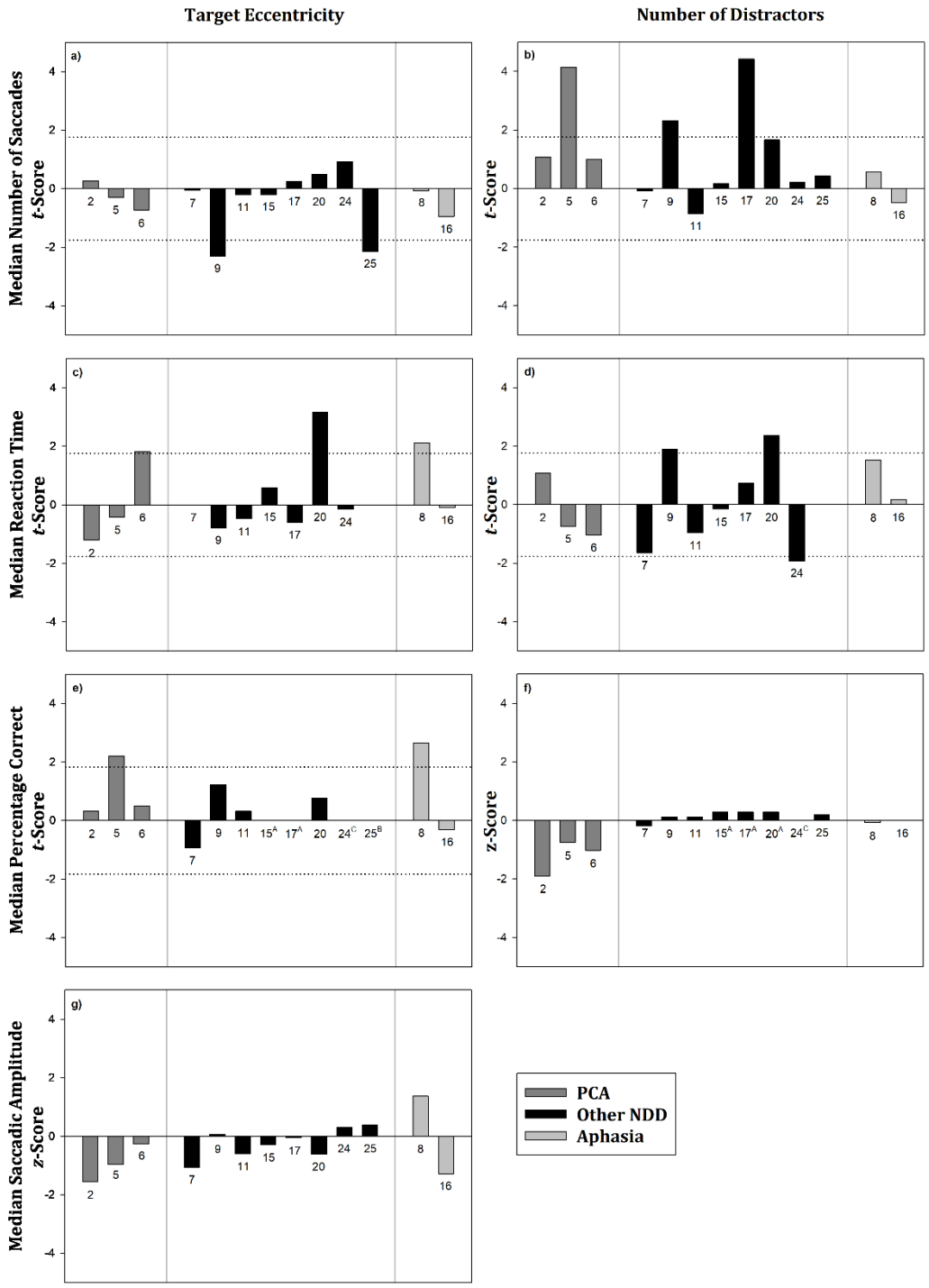


Figure 5.9: Slope Comparison Analysis *t*-Scores (a-e) and Patient *z*-Score (f-g) Plots
Key: · · · · · represents upper and lower critical value of *t.*
Subscripted labels refer to patient number.
[A] Accuracy was constant at 100%, therefore no slope was calculated. [B] Accuracy was constant at 0%, therefore no slope was calculated. [C] Insufficient data were available for calculation due to data loss from the cleaning phase.
Note: Patient 1 is omitted as they did not complete the Conjunction Task.
Patient 18 is omitted due to insufficient data for analysis, as a result of data loss from the cleaning phase.

Considering first median number of saccades, target eccentricity appears to have little effect, with all patients, except two other NDD patients, demonstrating regression slopes close to the control slope (Plot a, Figure 5.9). Number of distractors, however, appears to have a much greater influence on the slope values. One PCA patient (patient 5) demonstrated a much steeper slope, indicating a greater number of saccades made with increasing numbers of distractors (Plot b, Figure 5.9). Interestingly, around half of other NDD patients demonstrated a similar pattern to PCA patients. The observation that increasing number of distractors has a more profound effect on number of saccades made than increasing target eccentricity may be driven by one of a number of factors (discussed in Section 5.2.3.1, above). It is possible that this behaviour is the consequence of simultanagnosia, or due to the application of a different task set from controls. Qualitatively, controls were observed to apply a methodical search strategy to stimuli with large numbers of distractors. Patients may therefore not be applying top-down search strategies in the completion of this task.

Patient slopes for median RT (for correct trials) do not deviate notably from the control slope for increasing target eccentricity (Plot c, Figure 5.9). This is particularly interesting, as the prediction would be that patients with PCA (who often show simultanagnosia) would be expected to have dramatically greater reaction times to controls as a consequence of their narrowed attentional window, requiring a greater number of saccades in order to inspect every item on screen in order to determine the target location. One PCA patient (patient 6) behaved in this manner, but the other PCA patients were similar to controls. Similarly, the majority of the other patients (both other NDD and aphasia) also demonstrated RTs close to controls, with just two exceptions. The same pattern was observed for increasing number of distractors – with patients performing around the level of controls (Plot d, Figure 5.9). This indicates that the RT cost of increasing numbers of distractors is approximately equivalent for patients as it is for controls.

Note that linear regression for median percentage correct was not possible for five control participants (29.41%) as these participants demonstrated constant scores of 100% across the levels of the dependent variables. Therefore slope comparison analyses and the resulting *t*-scores are based on those control participants for whom linear regression was possible as they showed a deviation in their accuracy scores across the levels of the conditions.

Slope comparison analysis was not possible for median saccadic amplitude, therefore *z*-scores are presented in Plot g (Figure 5.9). From this plot it appears that PCA patients generally make the shortest amplitude saccades. Other NDD patients generally performed similarly to controls, with patients 7, 11 and 20 making shorter amplitude saccades, similar to the PCA patients. Short amplitude saccades are considered typical of PCA, therefore these results are in line with prior literature.

The effect of target eccentricity on percentage correct responses was very similar to the control group slope across the patient groups, with the exception of one PCA patient (patient 5) and one aphasia patient (patient 8), who demonstrated a greater effect of target eccentricity to controls (Plot e, Figure 5.9). This indicates that, for the majority of patients, performance was at a level similar to controls, with high levels of accuracy. However, an effect of increasing number of distractors was observed for all PCA patients, indicated in Plot f (Figure 5.9). Note that slope analysis was not possible for this dependent variable, therefore *z*-scores are plotted. All PCA patients performed worse than controls, which could indicate possible simultanagnosia (where patients fail to see the target with increasing number of distractors), although these results should be interpreted cautiously. Qualitative notes, taken at the time of assessment, detail that patients 16, 24, and 25 all required frequent support in recalling both the target and which button to press. These findings are reflected in the results (Figure 5.10, below), with patient 25 consistently pressing the opposite button and patient 16 failing to respond on the majority of trials.

Figure 5.10 additionally demonstrates that patient 24 is performing around the level of chance - therefore results from this patient cannot be interpreted further.

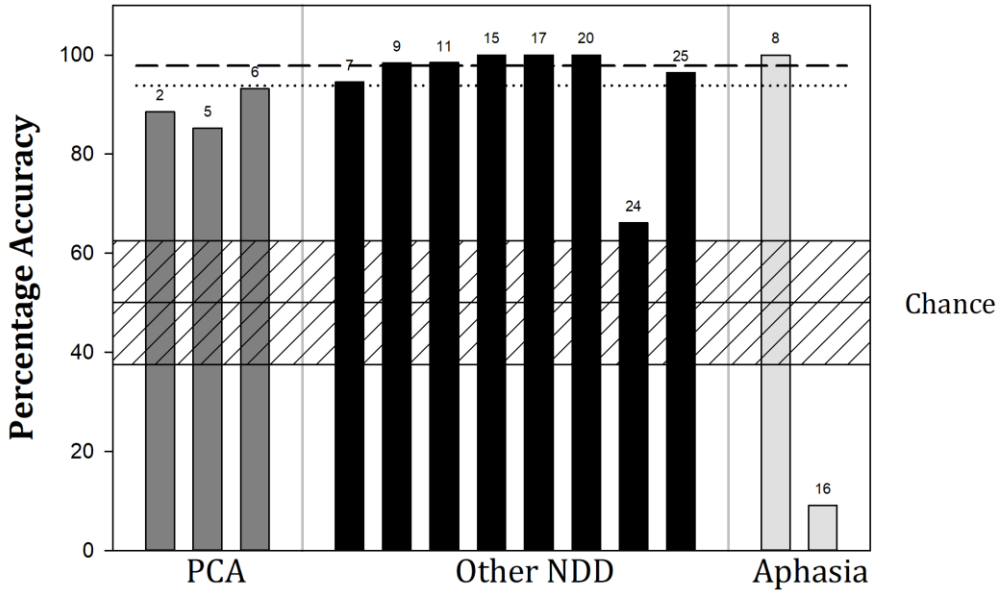


Figure 5.10: Bar Chart of Percentage Accuracy for Target Present Trials on Conjunction Condition
Key: — — — represents control mean, · · · · · represents lowest cut off for normal performance, shaded area within black lines represents upper and lower cut-off for performance at chance level.
Superscripted labels refer to patient number.
Note: Results for patient 25 are taken from a different response button, as this patient responded with the opposite button.
Patient 16 did not respond on 90.9% of trials.
Note: Patient 18 is omitted due to insufficient data for analysis, as a result of data loss from the cleaning phase. Patient 1 did not complete the conjuncton task.

5.3.3.3 Target Absent Trials

Target absent trials present a useful opportunity to establish what kind of overview patients have on the visual array. Results from target absent trials are discussed below, with control behaviour typified first, followed by analysis of patient performance

Control results were first analysed in order to characterise neurologically normal performance on this task.

The mean of median accuracy for controls in the target absent pop-out trials was 98.86% (SD = 1.41%) for the pop-out condition, and 97.99% (SD = 2.39%) for conjunction trials, therefore controls made very few errors on these trials and had a complete overview of the visual array. In order to establish whether there was any effect of number of distractors on accuracy, linear regression analyses were run. The results found that there was no effect of distractor number on accuracy for either the pop-out, $F(1, 100) = 0.117$, $p = 0.733$, or the conjunction condition, $F(1, 94) = 0.215$, $p = 0.644$. Controls therefore maintained a high level of accuracy regardless of how many stimuli there were on screen.

The mean of median RT for accurate trials was 766.71ms (SD = 131.79ms) for pop-out target absent trials, and 974.31ms (SD = 141.41ms) for conjunction trials. A one-way ANOVA indicated that the difference in RT between the conditions was significant, $F(1, 31) = 19.06$, $p = 0.000$ (Levene's test indicated equal variances, $p = 0.669$). In order to establish whether there was a significant effect of distractor number on RT for accurate trials, linear regression analyses were run. The results indicated that for pop-out trials, there was no significant effect of distractor number on accuracy, $F(1, 100) = 0.580$, $p = 0.448$, whereas for conjunction trials there was a significant effect of distractor number on RT, $F(1, 94) = 123.20$, $p = 0.000$. These are predictable results. Controls are quick to determine whether the target is present in pop-out trials, with few or no

saccades necessary in order process the array, whereas for conjunction trials controls must scan the array to discriminate whether the stimuli are targets or not, therefore increasing numbers of distractors would lead to greater RTs before an accurate response is made.

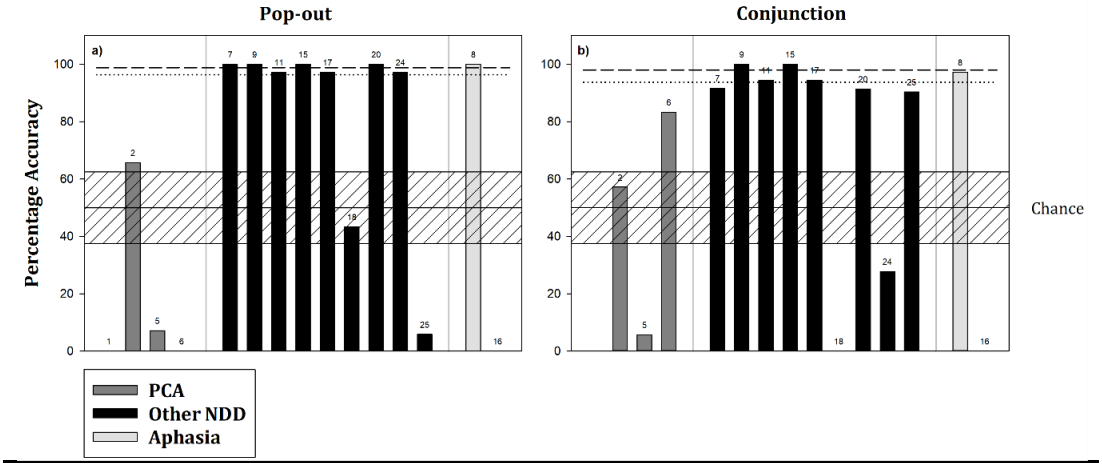


Figure 5.11: Percentage Accuracy for Target Absent Trials on Pop-out (a) and Conjunction (b) Conditions
Key: — — — represents control mean, · · · · · represents lowest cut off for normal performance, shaded area within black lines represents upper and lower cut-off for performance at chance level.
Superscripted labels refer to patient number.
Patient 1 did not respond on 60.7% of pop-out trials (and did not complete the conjunction task).
Patient 5 did not respond on 53.5% of pop-out trials, and 85.7% of conjunction trials.
Patient 6 did not respond on 91.2% of pop-out trials.
Patient 25 did not respond on 91.2% of pop-out trials.
Patient 16 did not respond on 96.6% of pop-out trials, and 96.6% of conjunction trials.
Patient 18 did not complete the conjunction task.

PCA patients demonstrate consistently inaccurate performance across the two conditions, with consistently high non-response rates. Patient 2 and patient 18 performed at chance level, therefore these patients are omitted from further analysis as they did not interact meaningfully with the task. High non-respondents are retained for further analysis. The high non-response rates of PCA patients, particularly in the pop-out task, further support the hypothesis that these patients apply a conjunction-like serial search in pop-out tasks, but experience the pop-out effect once the target is within the visual attentional window. The non-response may be due to patients repeatedly scanning the

visual array for the target, and failing to respond within the five-second time limit.

In contrast, the other NDD patients generally performed with accuracy levels close to those of controls, with the exception of patients 16 and 25 who had high non-response rates. As mentioned in Section 5.2.3.2, above, notes taken at the time of assessment of these patients suggest that they struggled to retain the button rules, therefore the high non-response rates observed may be due to a failure to comprehend the instructions.

Individual linear regression analyses were run for both patients and controls in order that slope comparison analyses could be performed, in order to compare patient performance to the control group on both accuracy and RT as a function of number of distractors for the pop out and conjunction conditions (Crawford & Garthwaite, 2004).

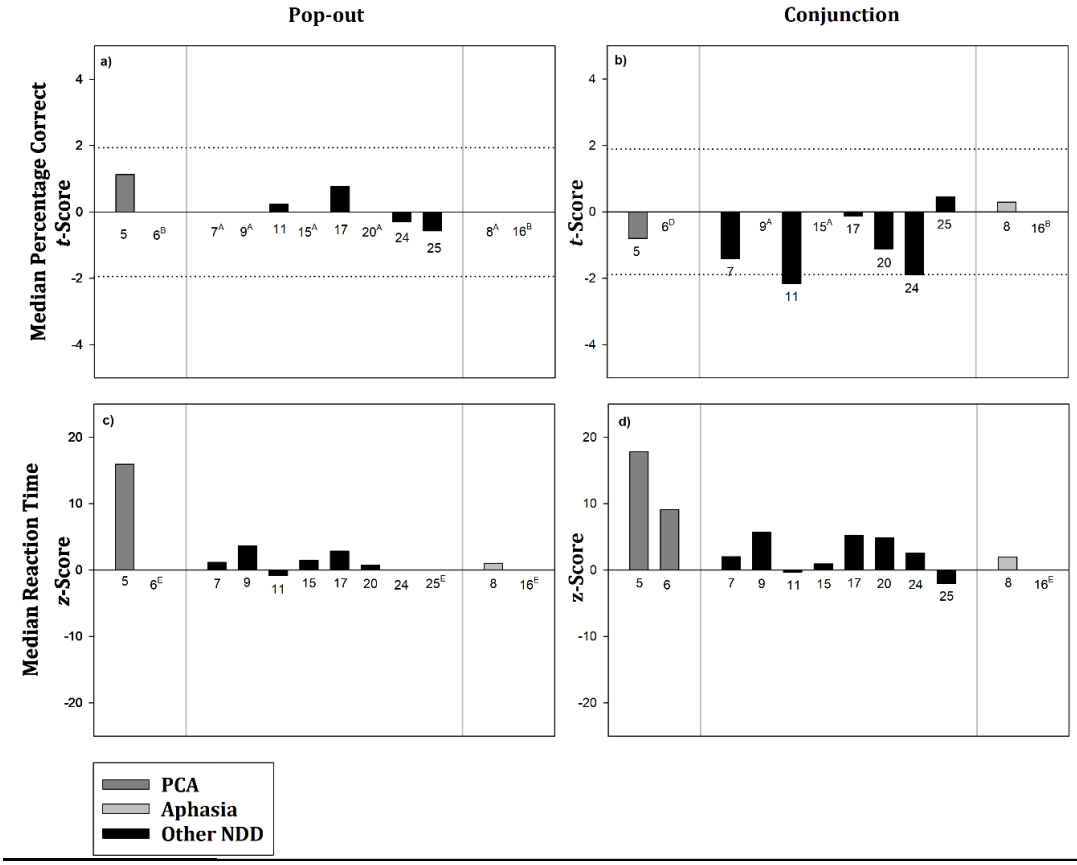


Figure 5.12: Slope Comparison Analysis *t*-Scores (a-b) and Patient *z*-Score (c-d) Plots
Key: · · · · · represents upper and lower critical value of *t.*
Subscripted labels refer to patient number.
[A] Accuracy was constant at 100%, therefore no slope was calculated. [B] Accuracy was constant at 0%, therefore no slope was calculated. [C] Insufficient data were available for calculation due to data loss from the cleaning phase.
[D] Accuracy was constant at 83.3%, therefore no slope was calculated. [E] No data were available for analysis due to high level of non-response.
Note: Patients 2 and 18 are omitted as they did not interact meaningfully with the task (see Figure 5.11).

Prior to considering the results of the accuracy slope comparison analysis, it should be noted that linear regression analysis was not possible for 10 control patients in the pop-out task (55%) and eight control patients in the conjunction task (47.5%) due to their scores being constant at 100% across the levels of the distractor condition. Therefore, slope analysis for median percentage correct is based only on those controls who showed some deviation in scores where linear regression was possible. Additionally, it should be noted that *z*-scores, particularly when they are applied to a task where the control group perform consistently at ceiling level, can be subject to compression effects where the SD is underestimated, and as a result the *z*-scores may be inflated. The

consequence of this is that impairment in patients may appear artificially high. Caution should therefore be exercised when interpreting these plots (Figure 5.12, Plots e-d). For clarity, Figure 5.13 is provided below which presents a more accurate overview of patient RT data.

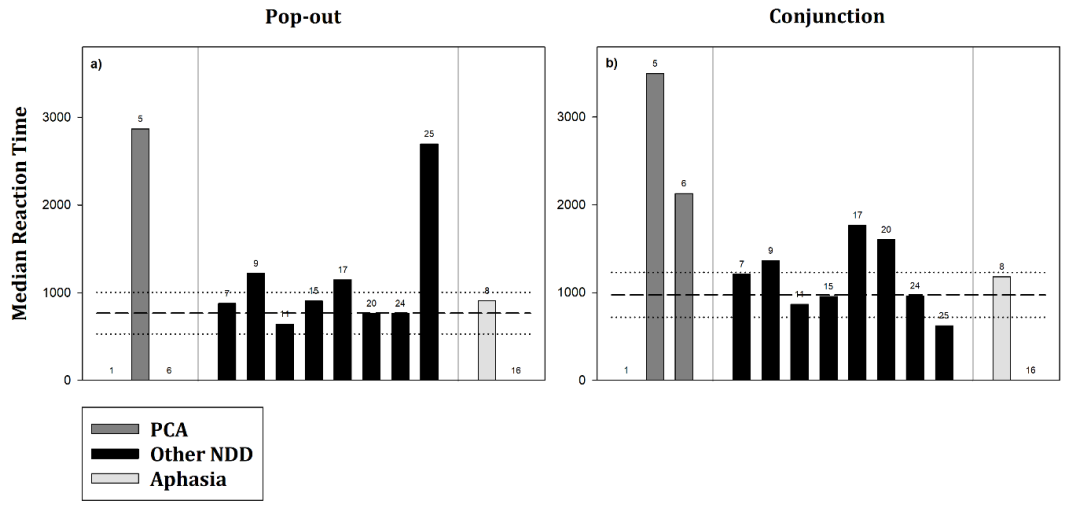


Figure 5.13: Median Reaction Time for Target Absent Trials on Pop-out (a) and Conjunction (b) Conditions
Key: — — — represents control mean, · · · · · represents upper and lower cut off for normal performance,
Superscripted labels refer to patient number.
Insufficient data were available for the calculation of median RT in the pop-out condition for patients 1, 6, and 16; and in the conjunction condition for patients 1 and 16 due to data loss from the cleaning phase and high levels of non-response, respectively.
Note: Note: Patients 2 and 18 are omitted as they did not interact meaningfully with the task (see Figure 5.11).

The PCA patient group demonstrates interesting patterns of behaviour. Patient 5 is consistently impaired across the conditions, with poor accuracy compared to controls for both the pop-out (Figure 5.12, Plot a) and conjunction conditions (Figure 5.12, Plot b), and longer RTs compared with controls in both conditions (Figure 5.12, Plot c-d). In contrast, patient 6 demonstrates perfect accuracy for the pop-out condition, and very high accuracy in the conjunction condition, suggesting that this patient has preserved visual discrimination abilities. However, this patient also demonstrates extended RTs compared with controls in the conjunction condition (Figure 5.12, Plot d). These longer RTs may be a consequence of simultanagnosia leading to a reduced visual attentional window,

as proposed in Section 5.2.3.2, the consequence of which is that patients take longer to scan and process the visual scene in order to identify whether the target is present.

The other NDD patient group was divided in the pop-out condition in terms of accuracy – with half of the patients performing at ceiling level (similar to the 8 control patients who also performed at ceiling level), and half demonstrating slopes which differed from the control group, thus showing a level of impairment, although this impairment is arguably very small (Figure 5.12, Plot a). However, these patients were generally much less accurate in the conjunction condition, with much greater slope coefficient deviations from the control group (Figure 5.12, Plot b). Median RTs for this group were around control levels for the pop-out task, but greater than controls for the conjunction task (Figure 5.12, Plot c and d, respectively, and Figure 5.13). This may indicate that these patients applied a different search strategy to controls in the conjunction task, which was perhaps less efficient, causing RTs to be inflated. These inflated RTs were also observed for target-present conjunction trials (Figure 5.12, Plot d) – which further supports the hypothesis that these patients may be applying a less ecologically valid search strategy than controls. This is additionally supported in both the target-present and target-absent trials by the observation that the other NDD patients generally show a good level of accuracy in the conjunction task (Figure 5.12 Plot b, and Figure 5.11), therefore, these patients are able to successfully discriminate whether the target is present or not, but they take longer than controls to ascertain this.

The aphasia patients, as a group, were also divided with patient 8 performing around the level of controls across the conditions (Figure 5.12, Plots a-d), and patient 16 demonstrating high levels of impairment (Figure 5.12, Plots a-b). It was not possible to plot RT data for patient 16 due to the high levels of non-responding, which in itself implies a high level of impairment.

5.4 Bisection Tasks

5.4.1 Procedure, Materials & Measures

The bisection task was a computerised version of the traditional paper-and-pencil line bisection task. There was an additional, somewhat novel, condition of 'gap' bisection (further details below).

The tasks were custom programmed in C++ and presented to participants using and HP Envy Rove Touchscreen Computer (active display area 423.33 x 238.13mm, resolution 1600 x 900 pixels).

Line bisection was presented to participants first. Participants were instructed to touch the line on the screen at the exact midpoint. When participants touched the line, it disappeared from view and the experimenter manually advanced to the next trial using a key press on a wireless keyboard. The second condition was gap bisection. In this condition patients were presented with two white dots on screen, which represented the two endpoints of an 'invisible' line. Task instructions were the same for both conditions. Participants were instructed to touch the screen at the location between the endpoints, which represented the exact midpoint of the visible, or invisible, line. Figure 5.14 presents example stimuli from each condition.

Line condition Gap condition

Figure 5.14: Line and Gap Bisection: Example Stimuli

Both the line bisection and gap bisection conditions consisted of the presentation of 6 repetitions of 4 different line stimuli. Each of the four stimuli varied in terms of the displacement (from the midline of the screen) of the left and right endpoints, either 'near' (± 27.6mm from midline) or 'far' (± 55.2mm from midline). The vertical range of stimuli was 50mm above the centre to 50mm below screen centre. Stimuli were 2mm thick white lines (or dots, in gap bisection) presented on a black background which was maximised to full screen.

The screen was cleaned for each participant in order to prevent smudges or fingerprints from influencing response behaviours. Patients completed this task as part of the screening battery of tests, and all patients completed the task in their own homes (except one patient who completed the screening assessments in a private lab space at the University of Edinburgh's Department of Psychology). For this reason only approximate viewing distances of 57cm were possible when testing patients, whereas a viewing distance of 57cm was measured and maintained when testing controls in the Human Movement Laboratory.

5.4.2 Analysis

In order to interpret these data, initial individual linear regression analyses were conducted for each patient and control across both conditions (line and gap) in order to establish whether the left and right endpoints of the stimuli significantly influenced the response position.

The dependent variables of interest for this task were calculated using the method outlined in McIntosh, Shindler, Birchall & Milner (2005). These dependent variables were used in order to compare their utility for assessing deficit, contrasted with the traditional method of using directional bisection error (DBE) (Guariglia, Matano & Piccardi, 2014; Sperber & Karnath, 2016).

The first of the alternative dependent variables was the 'endpoint weightings bias' measure (EWB). This was calculated using the following formula, where DPR is the change in response position given the rightmost endpoint of the stimulus, and DPL is the change in response position given the leftmost endpoint of the stimulus.

$$EWB = (DPR - DPL)$$

The ideal value of EWB is zero. Positive values indicate a greater influence of the right endpoint, and negative values indicate a greater influence of the left endpoint (McIntosh, Shindler, Birchall & Milner, 2005).

In addition to the EWB, the 'endpoint weightings sum' (EWS) was calculated using the following formula:

$$EWS = (DPR + DPL)$$

The EWS is hypothesized as a measure of the total attention the participant is giving to the task. If a participant is fully attending to the task, and is therefore influenced equally by the changing positions of both the left and the right endpoints, then the EWS should be 1. When unequal weightings are given to the left and the right endpoints of the stimuli (for example, in patients with left neglect who may fail to attend to the left side of the stimulus), the EWS will be less than one (McIntosh, Shindler, Birchall & Milner, 2005).

5.4.3 Results

Initial analysis of this task using DBE is presented in Chapter 4, Section 4.3.7.1. The aims of the more elaborative analysis presented below were twofold.

Primarily, these analyses were intended to assess the utility of EWB and EWS as alternative measures of bisection performance for patients with PCA. The secondary aim of these analyses was to investigate the usefulness of touchscreen-based bisection tasks as a test of general attention, rather than simply a test of lateralised visual attention.

Figure 5.15, below, presents the traditional bisection task dependent variable: directional bisection error (DBE).

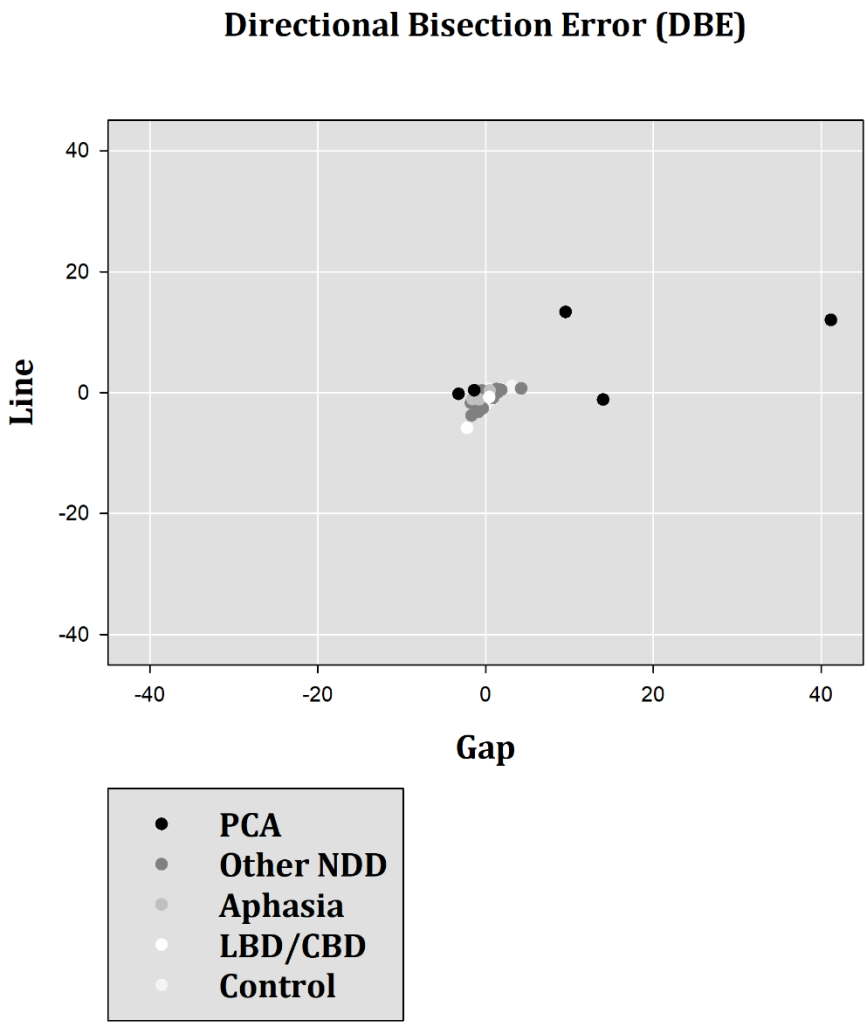


Figure 5.15: Directional Bisection Error: Line and Gap Condition

Figure 5.15 demonstrates a clustering of responses around zero, with three outliers, all of whom are PCA patients. Therefore, on this measure, PCA patients

are the only ones who appear impaired, compared to controls, making large rightward errors (possibly indicative of left visual neglect).

In order to assess how much of the variance from the linear regression analyses is explained by the left and right endpoints of the stimuli in each condition, Figure 5.16 presents plots which illustrate patient regression data. Both the controls and the majority of patients show a very high R^2 value (>0.7), indicating that the regression between response position (DV) and the left and right endpoints of the stimuli (IVs) explained most of the variance.

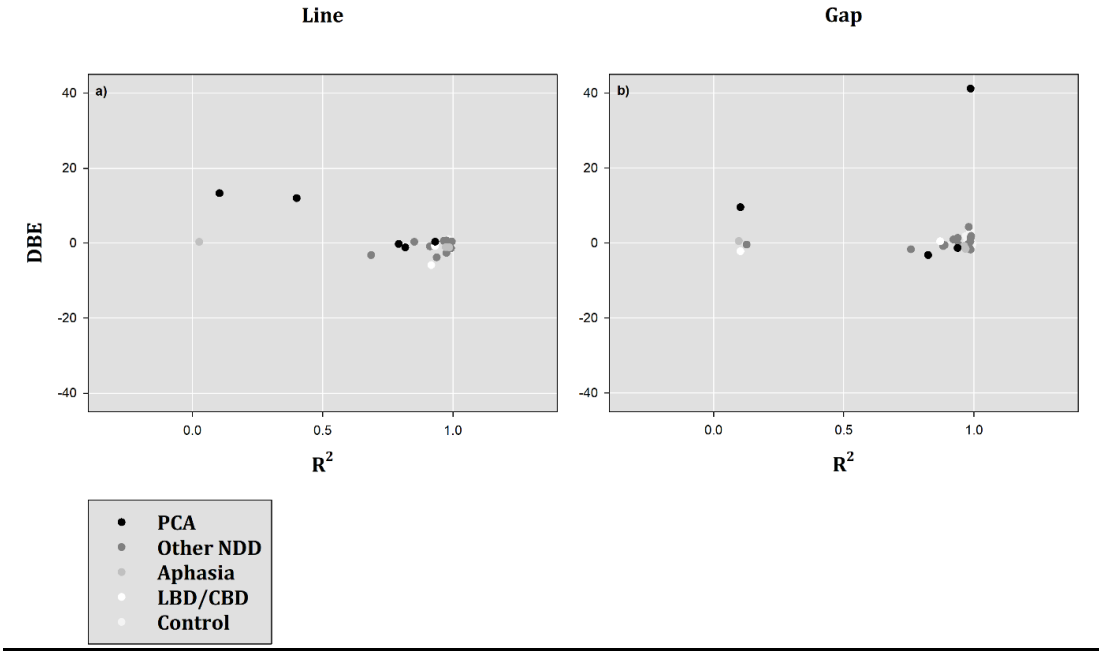


Figure 5.16: Directional Bisection Error: Line and Gap Condition

In the line task (Figure 5.16, Plot a), there are three anomalous patients, for whom less than half of the variance is explained by the changing endpoints of the stimuli - indicative of an insensitivity to the endpoints of the stimuli for these patients, so it is therefore assumed that they are not interacting meaningfully with the task. Similarly, in the gap task (Figure 5.16, Plot b), a clear bimodal distribution emerges with 4 patients with an R^2 of less than 0.5, and the remaining patients and controls demonstrating very high R^2 values (>0.6). This plot also reveals a particularly interesting case – a PCA patient (Patient 4) who has a near perfect R^2 but an abnormally large DBE. This could represent a real

instance of neglect. Following inspection of Figure 5.16: the data were cleaned according to the exclusion rules detailed in Table 5.5, below.

Dependent Variable	Exclusion Rule	Justification	Case(s) Excluded (Condition(s): Group)
N/A	If all of the trials are not completed in a condition, exclude all DVs for this condition	Given that each condition contains only 24 trials (6 repetitions of 4 different endpoint positions), missing data may cause bias in the EWS and EWB calculations.	5 (Gap: PCA)
R^2	If R^2 is less than or equal to 0.5, exclude the parameters of EWS and EWB	An R^2 of less than 0.5 indicates that less than half of the variance of the regression between mean response position and the left and right endpoints of the stimuli is explained. Therefore, in these instances participants cannot be assumed to be interacting meaningfully with the task.	1 (Line, Gap: PCA) 4 (Line: PCA) 12 (Gap: LBD/CBD) 16 (Line, Gap: Aphasia) 21 (Gap: Other NDD)

Table 5.5: Pop-out & Conjunction Task: Data Cleaning Exclusion Criteria

Individual trial responses for each stimulus are presented in Figure 5.17, below, for each patient who failed the R^2 data cleaning exclusion. These are presented in order that any interesting emergent patterns of behaviour may be identified. In addition, PCA patients who did not fail the R^2 data cleaning are presented (Figure 5.17, Plot x1-x4), in order to provide a complete overview of PCA patient behaviour in these tasks, given that the focus of much of this analysis is to typify PCA patient performance.

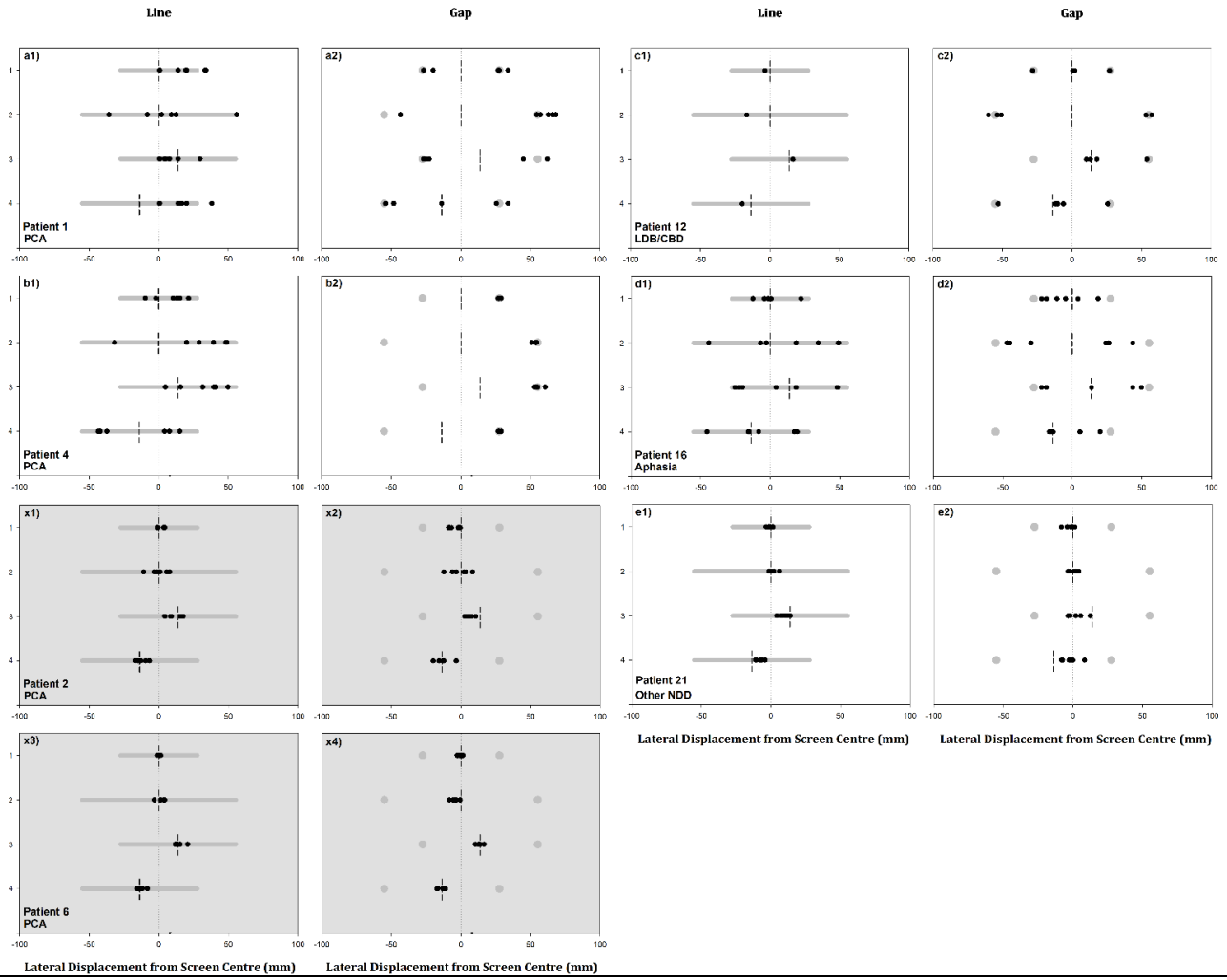


Figure 5.17: Individual Response Data for PCA and 'Abnormal R^2' Patients

Note: Dotted grey line represents screen midpoint, dashed black line represents true stimulus midpoint. Grey background plots present PCA patients with an R^2 score which was not deemed abnormal.

These individual response data indicate some striking patterns of behaviour, particularly from the PCA patients who did fail the R^2 data cleaning exercise. Patient 1 demonstrates a great deal of variability in their responses in the line condition, with a consistently strong rightward bias (Figure 5.17, Plot a1), which may be indicative of left visual neglect. This patient does not appear to be processing the endpoints of the lines properly in this task, occasionally responding beyond the end of the lines. In contrast, this patient demonstrates a clear bimodal distribution of responses in the gap task, with responses consistently on, or very close to, the endpoint stimuli - but never over-shooting the end of the stimuli as in the line task (Figure 5.17, Plot a2). Note that this patient could complete neither the assessment for OA nor extinction by confrontation, reporting an inability to see the stimuli. It is possible that the line and gap bisection results from this patient are indicative of an extremely narrowed attentional window – which, additionally, would provide some insight into their deficits in the OA and extinction task – the result of which being that the patient is unable to process the on-screen stimuli properly.

Patient 4 also shows a strong rightward bias in the line task, indicative of left visual neglect (Figure 5.17, Plot b1), but perhaps most striking is this patient's responses in the gap task, which are consistently on the rightmost endpoint stimulus (Figure 5.17, Plot b2). This is suggestive of extreme simultanagnosia, emerging in the gap task as a consequence of the endpoints of the stimuli appearing as two separate objects in the visual space. These results explain why this patient demonstrated a near-perfect R^2 with an abnormally high DBE for the gap task - they are very sensitive to the changing rightmost endpoints of the stimuli (resulting in a high R^2 value), but are consistently responding at the extreme right end of the stimulus.

Patient 2 (Figure 5.17, Plot x1-x2) and Patient 6 (Figure 5.17, Plot x3-x4) demonstrate relatively unremarkable results in these tasks, with Patient 2 showing arguably more variation in responses across both tasks than Patient 6. Relating the apparently dichotomous results within the PCA group to earlier

screening tasks (specifically the BORB 1: Copying Task and M-LAST, see Chapter 4 and Chapter 7), patients 1 and 4 demonstrated clear and profound visuospatial processing and visuo-constructional impairments, whereas patients 2 and 6 appeared less impaired (although not completely unimpaired). It is possible, therefore, that bisection results from Patients 1 and 4 may represent typical behaviour from a more progressed picture of PCA. This hypothesis is further supported by qualitative results from the OA and extinction by confrontation examinations. Results from qualitative brain scan analyses of these patients, presented in Chapter 8, appear to add some support to this hypothesis, although not consistently.

Results from Patient 16 suggest that this patient responded randomly across the stimuli across both conditions, with no sensitivity to the changing endpoints apparent (Figure 5.17, Plot d1-d2). Patient 12 demonstrates relatively normal results on the line bisection task, however the gap bisection results from this patient are unusual. The responses from this patient appear to show a level of ability to detect the true stimulus centre – but with an additional inability to decouple their responses from the endpoints, occasionally this patient will respond by pressing the endpoint on either side rather than the midpoint. These results may be accounted for by an executive dysfunction rather than a visuospatial processing deficit, given that this patient does demonstrate an ability to process both endpoint stimuli and respond accurately (Figure 5.17, Plot c2). Results from Patient 21 indicate that this patient does not take full account of the changing endpoints of the stimuli. Their responses shift towards the true midpoints, but consistently fail to land on the true midpoint (Figure 5.17, Plot e1). In contrast, this patient shows a different behavioural relationship on the gap bisection task - responding consistently at the screen-centre, rather than the centre of the stimulus (Figure 5.17, Plot e2). These are intriguing results. The fact that the patient demonstrates an ability to process the visual stimuli in the line bisection task, and yet fails to follow this same behavioural pattern in the gap bisection task suggests that the two tasks may require separate visuocognitive processes to complete.

5.4.3.1 EWS and EWB as Alternative Measures of Bisection Performance

EWS is proposed by McIntosh et al. as a measure of overall attention, with 1 representing perfect attention and 0 representing no attention (McIntosh, Shindler, Birchall & Milner, 2005). EWB is proposed as a measure of lateral asymmetry (0 representing no lateral asymmetry, a negative value representing leftward asymmetry and a positive value representing rightward asymmetry) (McIntosh et al., 2005). Figure 5.18, below, presents patient data on both of these DVs as function of condition.

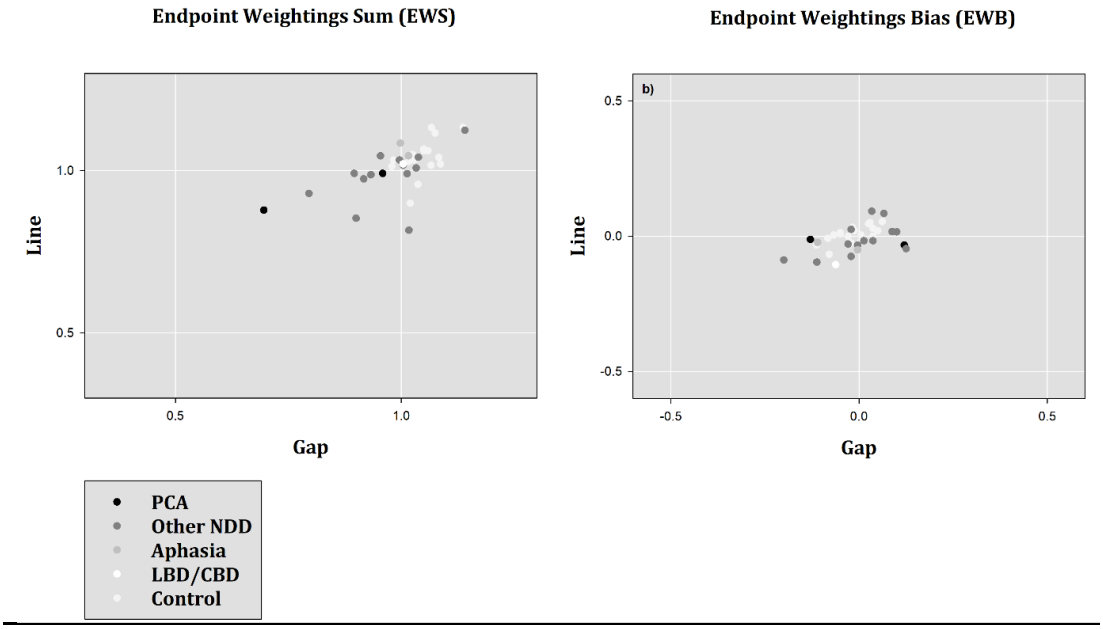


Figure 5.18: Directional Bisection Error: Line and Gap Condition

Generally, responses on EWS appear closely clustered around 1, with some outlying results. In order to test the relation of EWS between the two conditions Pearson correlation analyses were run. The results indicated a moderate correlation between line and gap EWS for controls, $r = 0.515$, n = 18, $p = 0.029$; and a moderate to strong correlation between line and gap EWS for patients, $r = 0.593$, n = 18, $p = 0.009$. Therefore total attention on the line bisection is moderately correlated to total attention on the gap bisection.

The gap condition appears to be accentuating the EWB, with a wider range of EWB values than in the line condition, which are more tightly clustered around 0. Evidence of a strong Pearson's correlation for controls (r = 0.672, n = 18, p = 0.002), and only a moderate correlation for patients between line and gap EWB (r = 0.473, n = 18, p = 0.047) suggests that the gap condition may be exposing an abnormality that the line condition is not. This can be compared to the DBE Pearson's correlation between the gap and line conditions, where a strong correlation between line and gap DBE was evident for controls, r = 0.647, n = 18, p = 0.004, and a stronger correlation between line and gap DBE for patients was observed, r = 0.776, n = 23, p = 0.000. This further suggests that the gap condition may target similar, but different, cognitive processes. For example, in order to successfully bisect the 'invisible' line on the gap condition, the viewer must first form a mental percept of the 'complete' line. Thus, it is feasible that gap bisection differs from line bisection due, in part, to the requirement of mental imagery as well as visual perception.

In order to get a better idea of individual behaviours, the relationship between EWS and EWB on both the line and gap task is plotted. It is possible that some patients may have responded by repeatedly touching one endpoint of the stimuli, rather than the centre point. Patients responding in this manner would have an EWS of close to 1, as they would be very sensitive to the changing endpoints of the stimuli. The associated EWB for these patients would be close to -1 for those who respond only to the very left endpoint of stimuli (neglecting the right side), or conversely, close to 1 for patients responding only to the right of stimuli (neglecting the left side). If responses are observed to be lateralised to only one side, it may represent magnetic-misreaching behaviour.

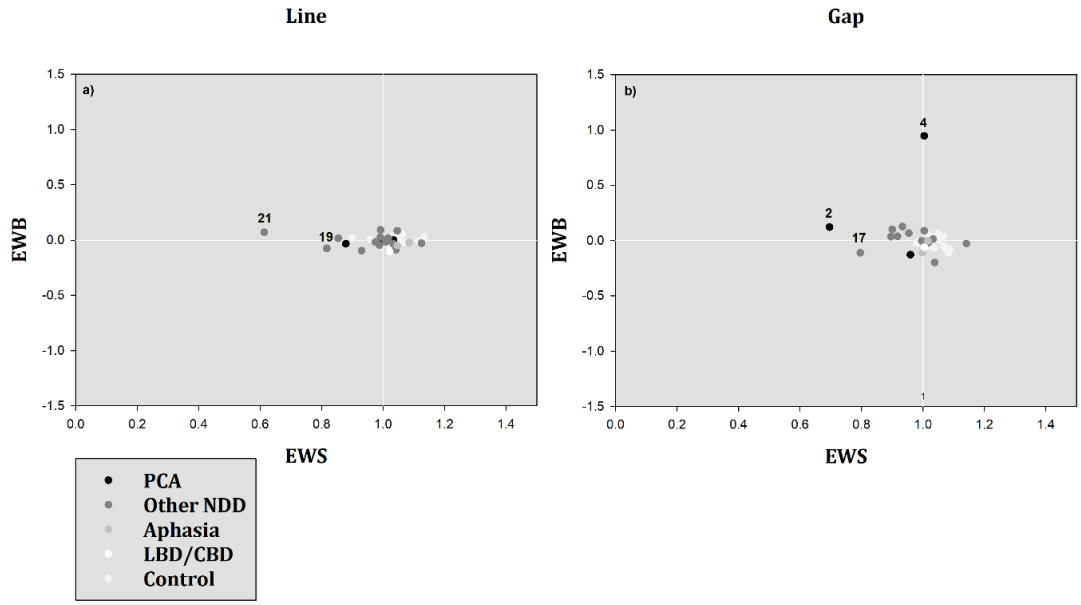


Figure 5.19: The Relationship Between EWS and EWB on the Line and Gap Task.
Note: Outlier responses are superscripted with the patient number.
The intersection of the white lines on each plot represents ideal performance.

The line condition does not appear to reveal much abnormality – with the exception of patient 21 who appears to have an abnormally low EWS (Figure 5.19, Plot a). This indicates a greater degree of insensitivity to the changing endpoints of the line than those participants whose EWS was closer to 1. Within the gap condition, the dominant influence of the right endpoint on responding for Patient 4 (as presented in Figure 5.17) is evident from the highly positive EWB with associated near-perfect EWS.

In order to formally compare the utility of the EWS and EWB measures as alternative dependent variables from bisection tasks, sensitivity, specificity and diagnostic accuracy values were calculated for both EWS and EWB, and contrasted with the same measures for DBE (previously reported in Chapter 4).

Cut-offs for normal performance on EWS and EWB were calculated for both the line and gap conditions, using the formulae specified in Section 5.4.2 of the present chapter. These results are summarized by diagnostic group in Table 5.6, below.

DV and Condition		PCA			Other NDD			Aphasia			LBD/CB		
		N	A	ND	N	A	ND	N	A	ND	N	A	ND
DBE													
	Line	3	2	-	11	3	-	3	0	-	1	1	-
	Gap	1	3	1	17	1	-	2	1	-	1	1	-
EWS													
	Line	2	1	2	9	5	-	2	0	1	1	1	-
	Gap	1	2	2	6	7	1	2	0	1	1	0	1
EWB													
	Line	3	0	2	8	6	-	1	1	1	0	2	-
	Gap	0	3	2	8	5	1	1	1	1	1	1	-

Table 5.6: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on the Line and Gap Bisection Task by Diagnostic Group
Note: N = 'normal', within the lower and upper cut-offs for healthy control performance. A = 'abnormal', outside the lower and upper cut-offs for healthy control performance, ND = No data available for calculation, indicating the number of patients within the full sample for whom no data were available.

Unfortunately, due to data cleaning processes, there are limited data available from PCA patients on EWS and EWB. Therefore the sensitivity and specificity values obtained must be interpreted with due caution.

DV and Condition		Sensitivity (%)	Specificity (%)	Diagnostic Accuracy (%)
DBE				
	Line	50.00	78.57	68.42
	Gap	75.00	78.57	77.78
EWS				
	Line	33.33	64.23	58.82
	Gap	66.67	46.15	50.00
EWB				
	Line	00.00	57.14	47.06
	Gap	100.00	61.54	68.75

Table 5.7: Sensitivity, Specificity, and Diagnostic Accuracy Calculations for Bisection Task

On the line task the DBE appears to be the most sensitive and specific, with poor sensitivity of 33% and 0% observed for the EWS and EWB, respectively, on this task (see Table 5.7). Similarly, DBE appears to demonstrate superior specificity to both EWS and EWB on the line task. However, in gap bisection we observe a different pattern. EWB is by far the most sensitive measure (100%), suggesting that EWB as a measure on this task will accurately detect true deficits. The DBE maintains the highest specificity (78.57) as in the line task. These results do

show some promise for use in a clinical setting to identify PCA-specific-deficits from other forms of dementia. In the present analysis, cut-offs for abnormality were generated using control data. However, in order for these tasks to be useful in a differential diagnostic context, it would be salient to generate cut-offs for abnormality by using patient data. Control participants are typically highly accurate on bisection tasks, thus cut-offs for normality generated from control data may be overly conservative when applied to patient data. Instead, generating cut-offs for normality using patient data allows the test to be 'titrated' to specific levels of impairment. For example, by generating cut-offs from a cohort of dementia patients, it may be possible to determine cut-offs for normality, which would make the test highly sensitive and specific to impairments associated with PCA (e.g. neglect).

Arguably, none of these measures (DBE, EWS and EWB) capture the striking behaviour observed by two of the PCA patients (Figure 5.17, Plots a1-b2). Although these data are exploratory, and limited in patient numbers, there appears to be an emergent pattern of behaviour, specific to PCA, and which gap bisection reveals, whereby patients will touch the endpoints of the stimuli rather than the mid-point between stimuli. This reinforces the argument for investigating the diagnostic utility of these tasks further, and for generating PCA-specific cut-offs for abnormality.

5.4.3.2 Touchscreen Bisection as a Test of General Attention

In order to assess whether bisection tasks may be a useful measure of general attention, Pearson's correlation analyses were run between TEA (elevator counting) and EWS for the line and gap bisection tasks for patients.

A moderate correlation was observed for patients on the line task, $r = 0.547$, n = 17, $p = 0.023$. In contrast, on gap bisection, the correlation did not reach a satisfactory level of statistical significance, $r = 0.392$, n = 16, $p = 0.133$.

These results indicate that line bisection may represent an alternative measure of general attention to the TEA, with EWS as the dependent measure. Observing no correlation between gap bisection EWS and TEA results further supports the findings, discussed above, that gap bisection may tap different cognitive processes to line bisection. Therefore, gap bisection does not appear to be a test of general attention, but is likely to represent a more nuanced assessment of visuospatial or visuoperceptual bias.

Line bisection EWS as an alternative measure of general attention to the TEA is a finding which would be deserving of further study. The TEA is poorly tolerated by patients who, through testing in the course of the present study, found the instructions to be complex and the task to be prohibitively long. Patients tended to perform at floor level on the subsequent conditions of the TEA (elevator counting with distraction, and elevator counting with reversal), making interpretation of these data impossible. In contrast – task instructions for the line bisection task were simple to explain, and the task quick and easy to administer. The nature of the bisection tasks mean that there is no 'floor level' of performance, so that any level of deficit on this task can be meaningfully interpreted. Touchscreen-based line bisection tasks may therefore represent a more rapid and less burdensome alternative measure of general attention, which could feasibly be used in clinics for assessment.

5.5 Cancellation Tasks

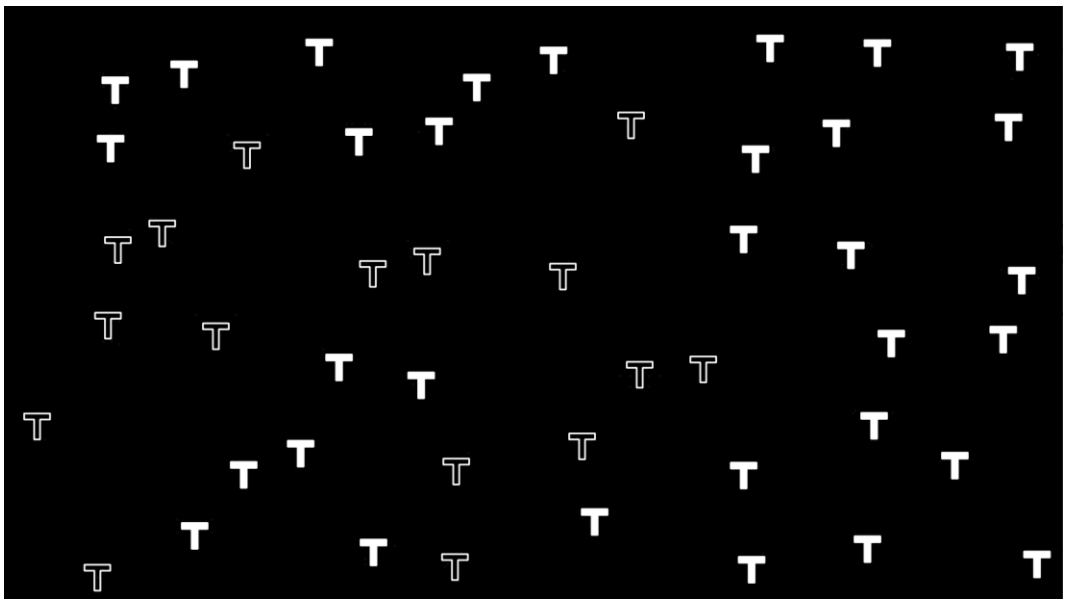
5.5.1 Procedure, Materials & Measures

The cancellation task was a touchscreen-based version of the apple cancellation task, using alternative stimuli in 'visible' and 'invisible' visual feedback conditions.

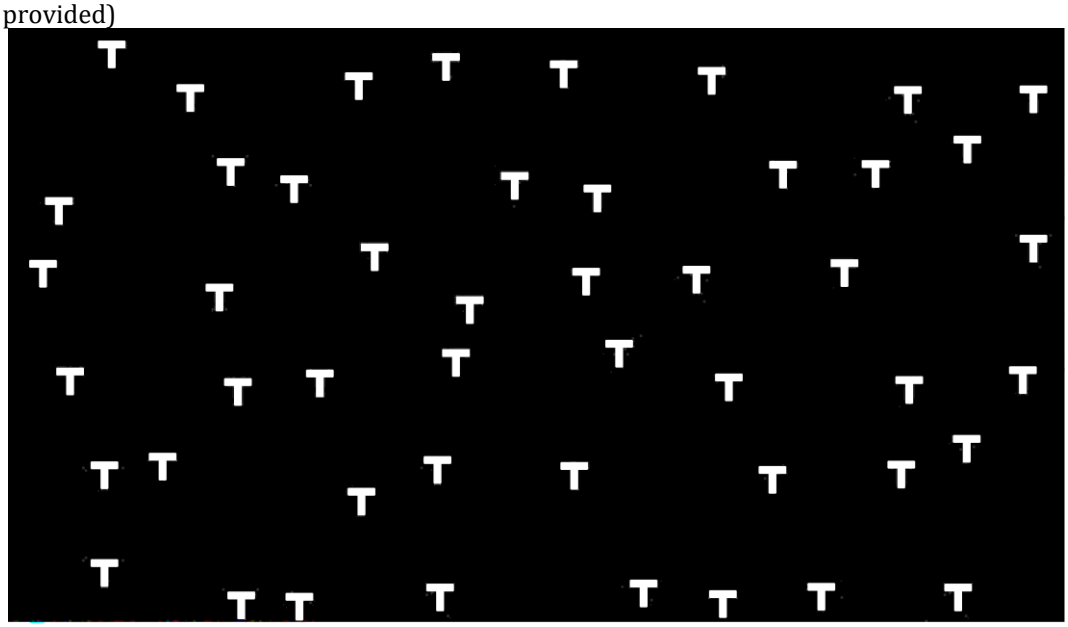
The two conditions of this task were presented separately, with the 'visible' condition always presented first. The task instructions (identical for both conditions) were to touch all 'T' shaped stimuli presented on screen, in any order, until each stimulus had been touched. Stimuli were presented simultaneously. Participants were instructed to use their dominant hand's index finger, and to tell the experimenter when they had finished. The task timed out automatically after 90 seconds if the experimenter had not been told that the participant was finished.

The stimuli were 48 white 'T' shapes (although they changed to a white 'outline' in the visible condition once touched), 15mm in height and presented on a black background which was maximised to full screen. Stimuli were organised around 8 columns and 6 rows on screen, but a jitter function within the program made stimuli appear evenly dispersed across the screen. The cancellation task was custom programmed in LabView and presented to participants using and HP Envy Rove Touchscreen Computer (active display area 423.33 x 238.13mm, resolution 1600 x 900 pixels).

As with the line bisection task above, after each participant the screen was cleaned, and was positioned approximately 57cm from the patient's eyes. Patients completed this task as part of the screening battery of tests and all patients completed the task in their own homes (with the exception of one patient who completed the screening battery at The Department of Psychology, in a private lab space).



Visible Condition ('T' shapes change from filled to unfilled when touched, visual feedback provided)



Invisible Condition ('T' shapes do not change when touched, no visual feedback provided)

Figure 5.20: Cancellation Task: Example Stimuli for Visible and Invisible Conditions (with visual feedback demonstrated).

The first condition was the 'visible' condition, whereby when participants touched the shapes they would change from solid white in colour to 'unfilled', with only an outline remaining (see Figure 5.20, above). This gave participants visual feedback on which stimuli they had touched. The second condition was the 'invisible' condition. The stimuli and task instructions were the same, but in this condition the stimuli did not change in appearance when touched, but instead remained solid white in colour. Therefore, visual feedback was withheld.

5.5.2 Analysis

The aim of these analyses was to determine whether other dependent measures, which can easily be recorded using a touchscreen-based cancellation task, are more sensitive and specific to PCA than simply target omissions (as reported in Chapter 4, Section 4.3.7.2). Prior analysis of target omissions within Chapter 4 found that patients tended to differ in their performance across the visible and invisible cancellation tasks, with PCA patients making significantly more omissions in the invisible condition. Sensitivity and specificity values for each condition were calculated using abnormality cut-offs generated using control mean data. The present analysis explores alternative dependent measures with suggested cut-offs for abnormality, determined with reference to patient performance. The dependent variables of interest in the present analysis were total time and median *x* co-ordinate.

Visual inspection of scatterplots between each condition was used to determine whether any clear group patterns of behaviour were apparent. For those variables where a distinction between diagnostic group behaviour was apparent, abnormality cut-offs are proposed and associated sensitivity, specificity and diagnostic accuracy values are presented.

5.5.3 Results

The cancellation tasks (both visible and invisible) appeared very sensitive to PCA – with PCA patients performing worse than all other patients and controls in every measure. Patients (not limited to PCA) appeared to perform generally worse than controls on most measures, with the exception of target touches and median *x* co-ordinate. Given these results, it seems logical to generate cut-offs for abnormality based on patient rather than control data, given that the overriding aim of this experiment was to determine its ability to discriminate PCA from non-PCA-type dementias.

From initial visual inspection, the most sensitive measures to separate PCA patients from patients in other diagnostic groups were total time and median *x* co-ordinate. In addition, target retouches appeared to be sensitive to PCA in the visible condition. These dependent variables are presented and discussed below, with proposed cut-offs and associated sensitivity, specificity and diagnostic accuracy values for total time and median *x* co-ordinate.

Figure 5.21, below, presents the 'stimuli-specific' dependent variables, touches (that is, targets touched) and retouches (targets touched more than once).

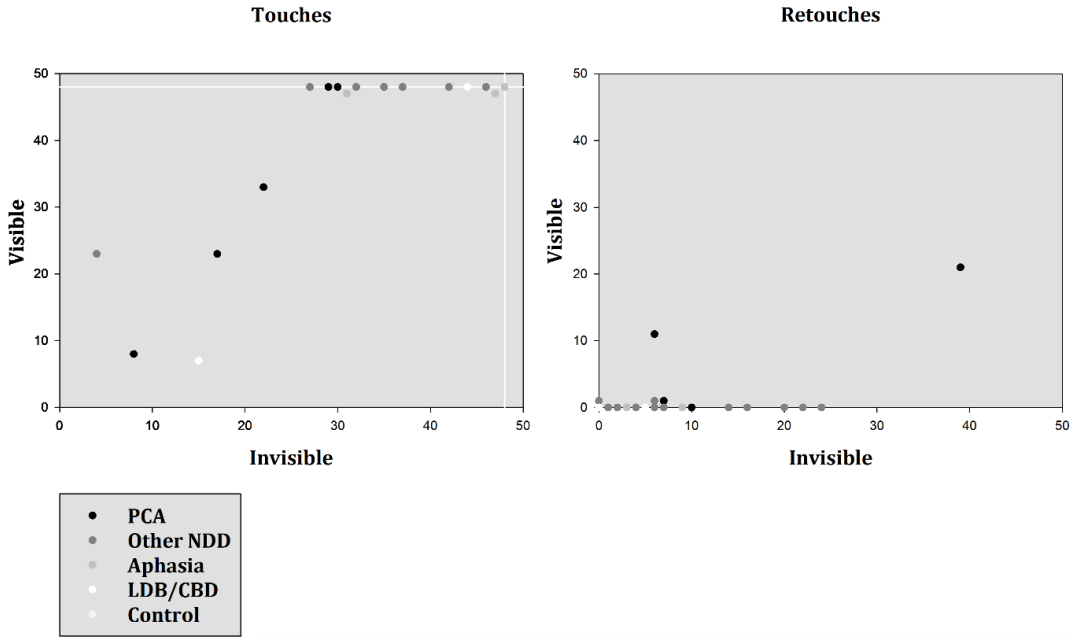


Figure 5.21: 'Stimuli-Specific' Cancellation Results
Note: The white line on the 'touches' plot indicates the total number of on-screen targets (48), and thus the maximum attainable score.

From these plots it is apparent that PCA patients perform worse than other groups on both measures. Clearly, cancellation tasks are generally sensitive to deficits related to PCA. However, there is a lack of specificity across these variables when compared to time taken and median *x* co-ordinate, presented in Figure 5.22, below.

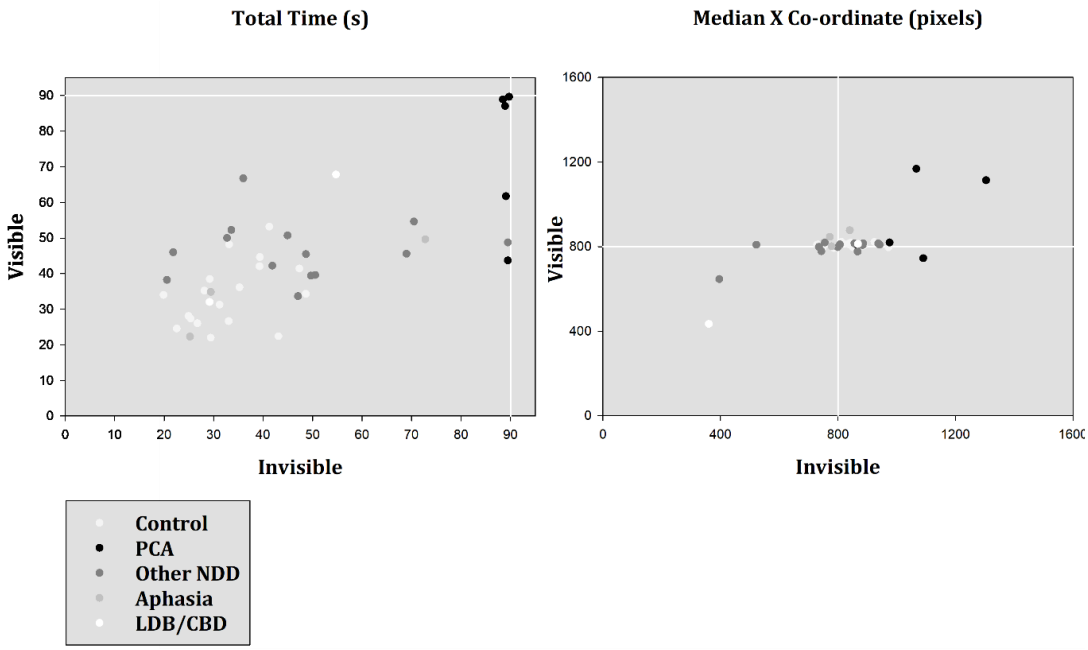


Figure 5.22: Total Time and Median *x* Co-ordinate Cancellation Results
Note: white lines on the 'total time' plot indicate the point at which the experiment times out (90 seconds); on the median *x* co-ordinate plot indicate screen centre.

A much clearer distinction is apparent between PCA patient performance and patients in other diagnostic groups on both the total time and median *x* co-ordinate measures.

PCA patients, almost without exception, are the only patients who continue to search the visual array for stimuli until the experiment times out – particularly for the invisible cancellation condition. This may indicate deficits in visuospatial working memory, which has been observed to be severely impaired in Bálint's syndrome patients and is associated with posterior parietal lobe damage (Berryhill & Olson, 2009; Berryhill, 2012). These patients may continue to search for targets because deficits in their visuospatial working memory mean that they are therefore not certain that they have seen and responded to the whole array. This apparently clear distinction between the behaviour of PCA patients and the behaviour of other patient groups make this measure of performance a good candidate to be used as an indicator of deficits related to PCA.

Similarly, almost all of the PCA patients demonstrated a rightward bias, as measured by median *x* co-ordinate. This bias is apparent in both the visible and invisible conditions, but is revealed more strongly in the invisible condition. This rightward bias is suggestive of left visual neglect.

Invisible cancellation appears therefore to be more revealing of PCA-specific deficits than visible cancellation. Total time and median *x* co-ordinates appear to be the most sensitive and specific measures. Cut-offs for normality are proposed for the two measures, with associated sensitivity, specificity and diagnostic accuracy values reported. Figure 5.23, below, presents cut-offs (*c*) for each measure and condition.

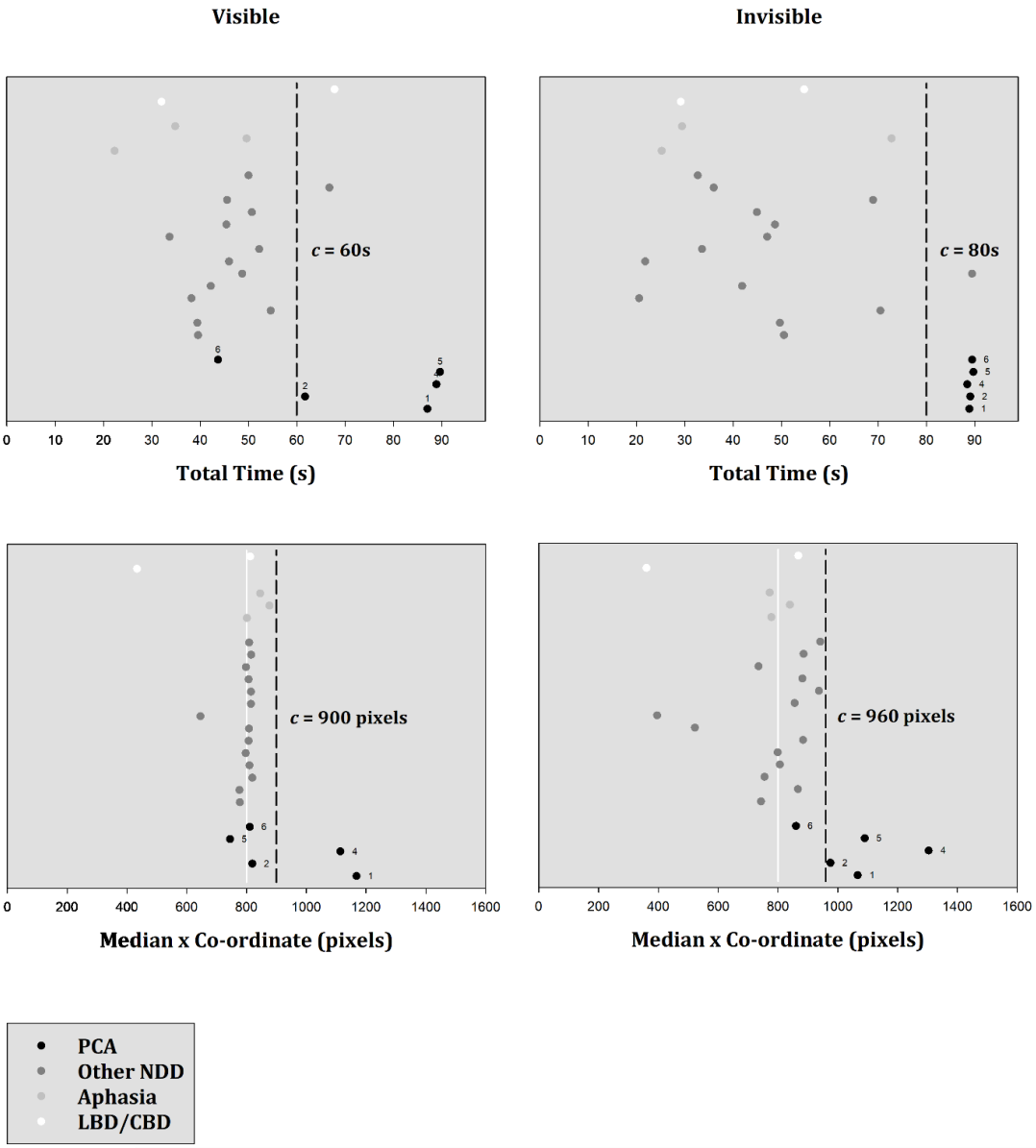


Figure 5.23: Proposed Cut-offs for Abnormality of Total Time and Median *x* Co-ordinate Measures

Key: — — — represents proposed cut-off value, white line on median x co-ordinate plots represents true screen centre, c = proposed cut off for measure/condition.
PCA patient numbers are presented for illustrative purposes.

DV and Condition	PCA			Other NDD			Aphasia			LBD/CB		
	N	A	ND	N	A	ND	N	A	ND	N	A	ND
Total Time												
Visible	1	4	-	13	1	-	3	0	-	1	1	-
Invisible	0	5	-	13	1	-	3	0	-	2	0	-
Median *x* Co-ordinate												
Visible	2	3	-	14	0	-	3	0	-	2	0	-
Invisible	1	4	-	14	0	-	3	0	-	2	0	-

Table 5.8: Frequency of Patients Performing Within Normal Limits or Performing Abnormally on the Invisible and Visible Cancellation Task by Diagnostic Group
Note: N = 'normal', below the cut-off for abnormal performance. A = 'abnormal', above the cut-off for abnormal performance. ND = No data available for calculation, indicating the number of patients within the full sample for whom no data were available.

Table 5.8, above, presents the abnormality frequencies for each patient group, using the proposed cut-offs for detecting PCA-like abnormality. Cut-offs were determined in order to produce the highest possible sensitivity and specificity values (see Table 5.9, below).

DV and Condition	Sensitivity (%)	Specificity (%)	Diagnostic Accuracy (%)
Total Time			
Visible	80.00	92.86	89.47
Invisible	100.00	92.86	94.74
Median x Co-ordinate			
Visible	60.00	100.00	89.47
Invisible	80.00	100.00	94.74

Table 5.9: Sensitivity, Specificity, and Diagnostic Accuracy Calculations for Cancellation Task

As a consequence of the left visual neglect observed in the PCA patients within this sample, median *x* co-ordinate offered a clearer distinction between PCA patients and non-PCA patients, therefore in this sample it was possible to generate a cut-off which would ensure that no non-PCA patients were classified as impaired. However, application of this cut-off may not prove as useful outwith this sample, as it is dependent on all of the PCA patients exhibiting symptoms of neglect. For this sample, the cut-off proposed for the median *x* co-ordinate dependent measure offers impressive specificity values of 100% for both the visible and invisible condition. Total time was less specific to PCA generally, however, the invisible condition appeared to offer the best

opportunity for high sensitivity and specificity values (100% and 92.86%, respectively).

Interestingly, visible cancellation search time was found to be significantly strongly correlated with mean search time for the pop-out visual search task on a Pearson's correlation, $r = 0.660$, n = 15, $p = 0.007$, which suggests that the visual search task and visible cancellation are related in terms of the visual processing demands required to complete them. Additional correlation analyses between visible and invisible cancellation and pop-out or conjunction mean reaction time did not reach a satisfactory level of statistical significance. This further supports the view that invisible cancellation requires additional processing beyond simple visual search (such as visuospatial working memory), and may therefore be more sensitive to deficits associated with PCA.

Relating the behavioural results from these measures to PCA performance in other tasks reported herein further supports the utility of invisible cancellation as a task to identify PCA-specific deficits. On visible median *x* co-ordinate only PCA patients 1 and 4 emerge as impaired (note that they presented with left-sided neglect on bisection, as well as left motor neglect). On the same measure under invisible task conditions, PCA patients 2 and 5 also exceed the proposed threshold of abnormality. Patient 5 exhibited symptoms of left visual extinction, and patient 2 demonstrated simultanagnosia in the extinction by confrontation task (but patient 2 additionally presented relatively normal bisection performance). Particularly of note are the results from patient 6, who appears relatively unimpaired compared to the other PCA patients on OA and extinction by confrontation, pop-out and conjunction visual search tasks, and line and gap bisection. However, this patient's behaviour emerges as 'anomalous' in the invisible cancellation total time measure, where they perform at the same level as the other PCA patients (whose performance is highly distinguishable from non-PCA patients).

5.6 Navon Task

5.6.1 Procedure, Materials & Measures

The Navon task was custom programmed using E-Prime. The task involved four conditions; a test condition consisting of the identification of large letters (to check that participants could reliably identify the largest letter forms that would be shown) as well as a field of small letters (to establish that patients could identify the letters in the smallest form), name local letter condition (name the small letters), name global condition (name the large letter), and a novel condition – name 'relief' (where participants were asked to name the large letter which was made of negative space, bordered by small letters). Only the letters 'H' and 'O' were used. This was to ensure that the letters were morphologically dissimilar from each other, and to ensure that the task was kept as simple and as brief as possible for those patients with known letter identification deficits (such as in the PCA patient group). The test condition was programmed to alert the experimenter if the participant made any errors within this condition. If errors occurred, the experimenter would re-run the field test. If patients made errors during the second field test run, then the test was abandoned because a satisfactory level of reading ability to ensure meaningful results had not been achieved.

The stimuli were drawn using Microsoft Paint and were the same height and width in pixels across the H and O conditions (55 x 39 pixels for the small letters, 360 x 280 pixels for the large letters). Global letters were formed of local letters (see Figure 5.24 below for stimuli).

The test condition consisted of 6 total stimuli, each presented twice. Large black stimuli were shown as well as large white stimuli, and were presented on a grey background in order to simulate the luminosity profile of the assessment relief stimuli.

The name local and name global assessment stimuli consisted of 4 unique stimuli (one for each available combination of congruent or incongruent local and global letters) presented 4 times per block. In addition, there were 4 unique relief stimuli (one for each possible combination of congruent and incongruent local and global letters, as above). In the relief condition, participants were instructed to name the 'largest letter', made of negative space. The name local, name global and name relief assessment conditions consisted of 2 blocks, therefore a total of 32 stimuli were presented in each condition (with each stimulus appearing 8 times). The task was programmed with a 20 second timeout function, after which time participants were asked to guess the answer (forced choice).

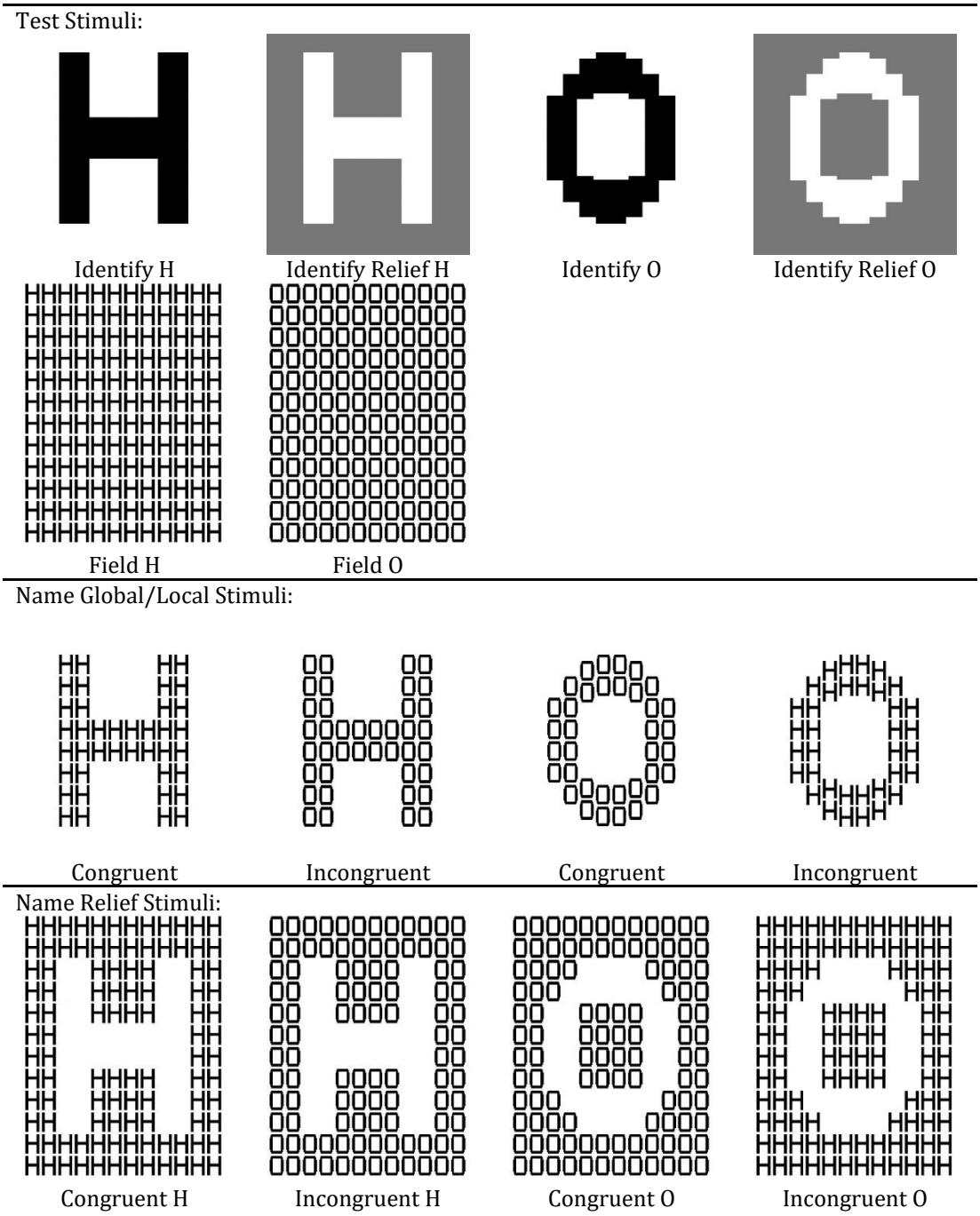


Figure 5.24: Navon Task: Example Stimuli

Task instructions were provided at the start of each condition. Participants were instructed to click the response button (held in their dominant hand) as soon as they knew what the answer was. They were then asked what the correct response was and the experimenter manually entered this into the program. For

example, in the global condition, participants were asked to "name the large letter".

The monitor was presented to participants at a viewing distance of 57cm in a fully-lit laboratory.

5.6.2 Analysis

In addition to the data cleaning rules applied (see Table 5.10, below), test trials were removed from further analysis.

Dependent Variable	Exclusion Rule	Justification	No. of cases excluded (% of total trials)
RT (anticipation)	RT of <250ms were coded as anticipatory, and therefore the trial was removed from further analysis	RTs which had a value of <250ms were coded as anticipatory responses, and were removed.	3 (0.11%)
RT (guess)	RT of >5000ms were coded as guesses, and were therefore removed from further analysis	Visual inspection of RT histograms revealed that 98.3% of RTs were within 5000ms.	49 (1.75%)

Table 5.10: Navon Task: Data Cleaning Exclusion Criteria

No PCA patients were able to complete this assessment, failing to progress beyond the test condition. PCA patients 2 and 6 could not identify any letters, reporting that all they could see were black squares and triangles. Patient 4 was unable to locate the screen in space (as observed in the Posner task). Patient 5 appeared to be responding randomly, and therefore was unable to progress to the assessment conditions.

As a consequence, analysis of this experiment is restricted to results from other NDD and control participants. The first aim of these analyses is to establish whether other NDD patients demonstrate a global precedence effect, as typically observed in controls. The secondary aim is to establish whether the relief condition elicits the same global precedence (with RTs similar to the global

condition), or whether the local stimuli 'become global' in this task and interfere with the processing of the global stimuli – which would be associated with a RT cost. A cost to the perception of relief stimuli may be indicative of visual attentional deficits.

Ratio scores were generated which compared median RT on the local and relief conditions to the median RT on the global condition. This was intended to serve as a measure of the difference, or 'cost' of each condition when compared to the global condition. The following formulae were used in order to calculate the 'cost of local' (CoL) and 'cost of relief' (CoR) scores:

$$CoL = \frac{median\ RT\ for\ local\ condition}{median\ RT\ for\ global\ condition}$$

$$CoR = \frac{median\ RT\ for\ relief\ condition}{median\ RT\ for\ global\ condition}$$

A high CoL score would indicate a greater RT cost for the local condition when compared to the global condition. Similarly, a high CoR score would indicate a greater RT in the relief condition, compared to the global condition.

5.6.3 Results

Figure 5.25 provides an insight into the group-level mean accuracy on each condition of the task, with surprising results. Other NDD patients and controls did not appear to differ greatly on the name global and name relief conditions both within- and between-groups. Given that the task in the name relief condition was to identify the large white letter (equivalent to a global letter in the other conditions), it is perhaps not surprising that both patients and controls completed this with relative ease. What is rather striking is the poor level of accuracy observed for controls in the name local condition: where controls demonstrated accuracy at chance levels, with very little variation (as

evidenced by the very small standard deviation). Other NDD patients were just above the level of chance – but were generally more accurate than controls on this condition.

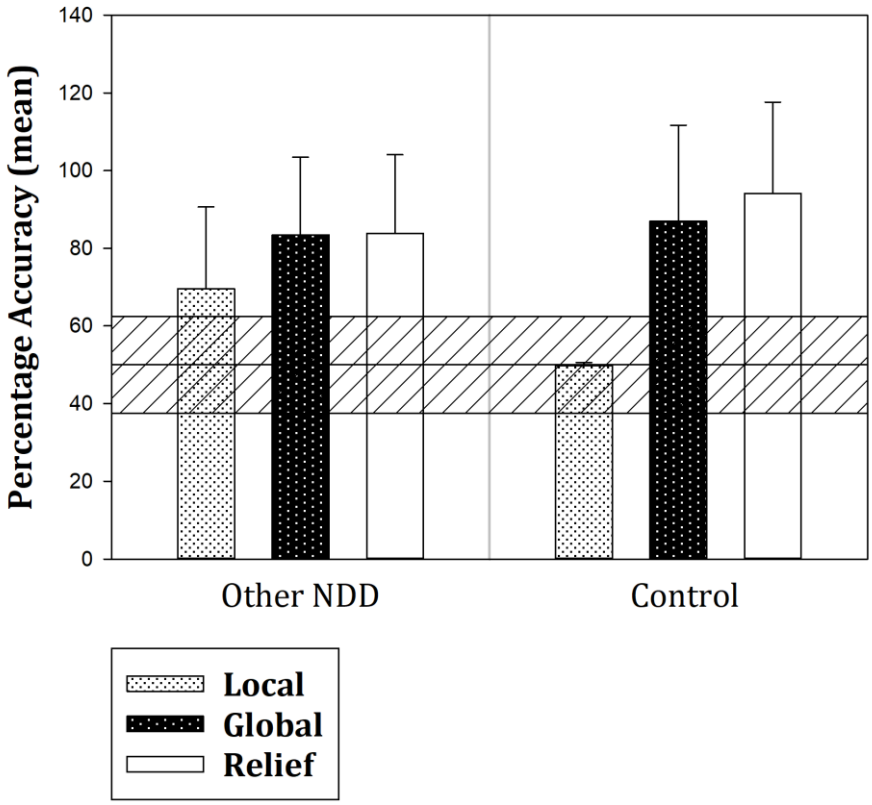


Figure 5.25: Mean Percentage Accuracy by Condition
Note: Error bars represent the standard deviation for that condition. Shaded area within black lines represents upper and lower cut-off for performance at chance level.

The poor accuracy observed for controls (and to some extent, for other NDD patients) could be due to participants responding with the global form, rather than the local from, which provides further support for the well-established hypothesis of global form precedence in visual processing. Performance at chance level for local form identification may also suggest that controls did not understand the task instructions correctly. However, qualitatively, it appeared during the course of testing that control participants were confident that they understood the task instructions: and these participants often responded very rapidly, which could also account for the poor accuracy.

A factorial ANOVA was conducted in order to compare the main effects of group and condition, as well as any group by condition interaction, on percentage accuracy. The results indicated a main effect of condition, $F(2, 69) = 12.897$, $p = 0.000$, indicating significant differences in percentage accuracy between the conditions. The interaction term was also significant, $F(2, 69) = 3.164$, $p = 0.048$, indicating significant differences between groups on different conditions. There was no main effect of group, $F(1, 69) = 0.154$, $p = 0.696$, indicating that other NDD and control participants did not differ significantly in percentage accuracy overall.

Post-hoc analyses were run in order to determine the significant simple main effects which drove the interaction, using a Tukey LSD correction. The results indicated that control percentage accuracy scores were significantly different between the local condition and both the global and relief conditions.

Figure 5.26 presents median reaction times for both groups under each condition. Other NDD patients appeared to have generally longer RTs than control participants. Control median RTs appeared consistent across each condition. In contrast, other NDD patients appeared to show the global precedence effect and, interestingly, this precedence for global forms was not supported in the relief condition.

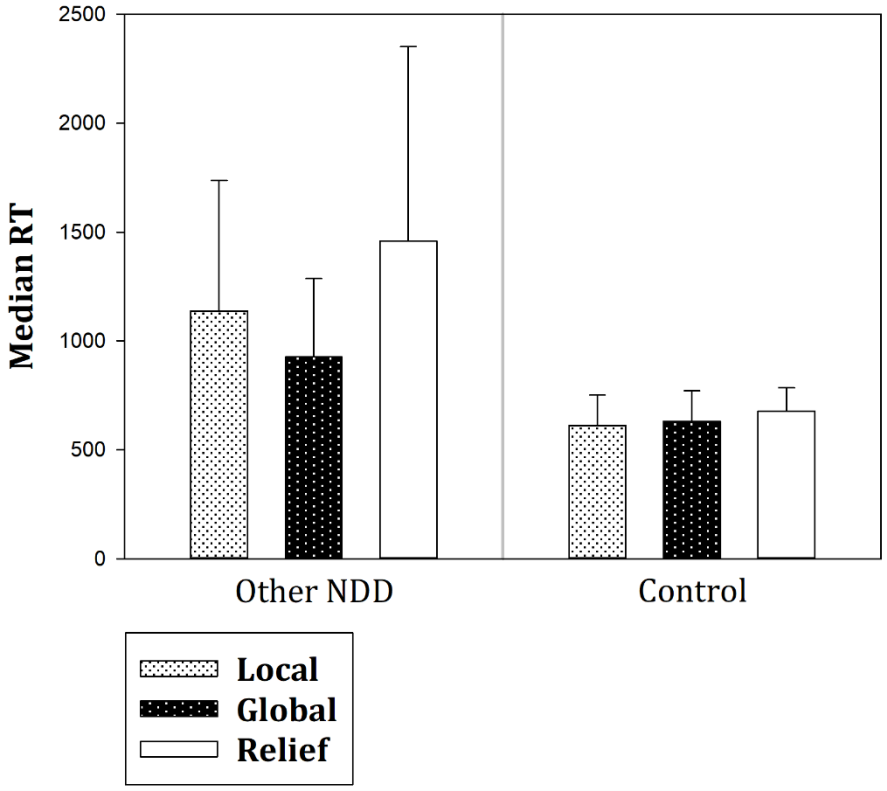


Figure 5.26: Mean Percentage Accuracy by Condition
Note: Error bars represent the standard deviation for that condition.

In order to assess this further, Figure 5.27, below, presents the CoL and CoR scores for each group.

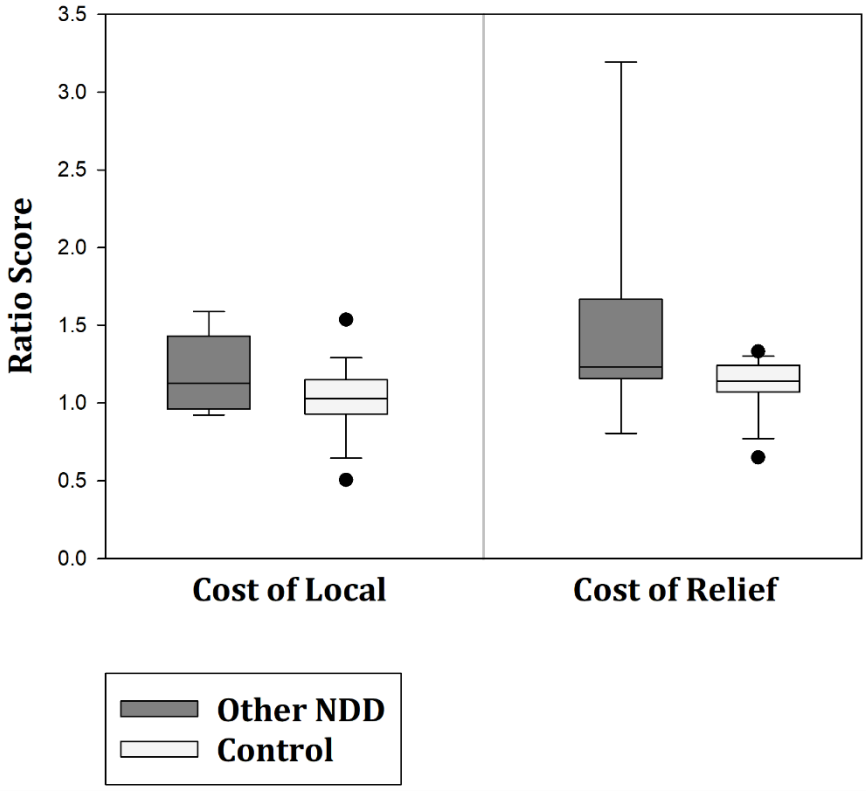


Figure 5.27: Mean Percentage Accuracy by Condition
Note: Error bars represent the standard deviation for that condition.

Figure 5.27 indicates that there was very little variability between other NDD and controls with regard to the cost associated with the local condition, with the majority of participants in both groups showing a low CoL, with a mean score indicating an approximately equivalent median RT between local and global conditions. A similar pattern was observed in the CoR score, with mean CoR scores indicating no difference between the relief and global conditions. However, there was more variability in responses from other NDD participants on CoR, which indicates that for some individuals there was a cost associated with relief over global processing. This suggests that the relief form is not necessarily processed in the same manner as the global form.

Higher RTs in the relief condition may be indicative of 'local' interference from the field of small letters which the large relief letter was formed within. Such local interference can be indicative of simultanagnosia, therefore the relief

condition may present a novel way to assess deficits in visual attention. Clearly, caution must be exercised when interpreting these results – which are rather speculative.

5.7 Posner Endogenous Attention Task

5.7.1 Procedure, Materials & Measures

A version of the classic Posner task (Posner, 1980) was programmed using E-Prime in order to test endogenous attention. Exogenous attention was not tested in this task, as it was necessary to keep the testing time in the lab to a minimum to reduce patient fatigue.

Participants were seated with a computer monitor 57cm from their eyes, in a blacked-out lab. They were given a button box and instructed to press the button whenever the green target appeared on screen. A demonstration screen was shown to participants so they could familiarise themselves with the target and the task instructions. Participants were advised that the central diamond would change into an arrow which – most of the time – would indicate the box in which the target would appear. This central 'diamond' shape changed as part of a fixation animation sequence, in which a fixation point appears to expand outwards from the centre to each point on the diamond, after which the directional arrow (cue) would appear. Fixation duration was randomised across trials, and was between 170 and 1170ms in duration. The cue target onset asynchrony was fixed at 550ms. Participants were also advised that, sometimes, no target would appear at all – in which instance they should not press any button. Figure 5.28, below, presents example stimuli from steps 1-3 of each trial, with congruent and incongruent target positions. Stimuli were presented at a resolution of 1024 x 768 pixels, and a refresh rate of 75Hz. After each response the experimenter manually advanced to the next trial using a key press.

There were 48 valid (congruent) cue trials, 16 invalid (incongruent) cue trials, and 16 catch trials (no target) per block. Participants completed two blocks, therefore in total there were 160 trials (96 congruent cues, 32 incongruent cues, and 32 catch trials). The proportion of targets to the left and right were equal.

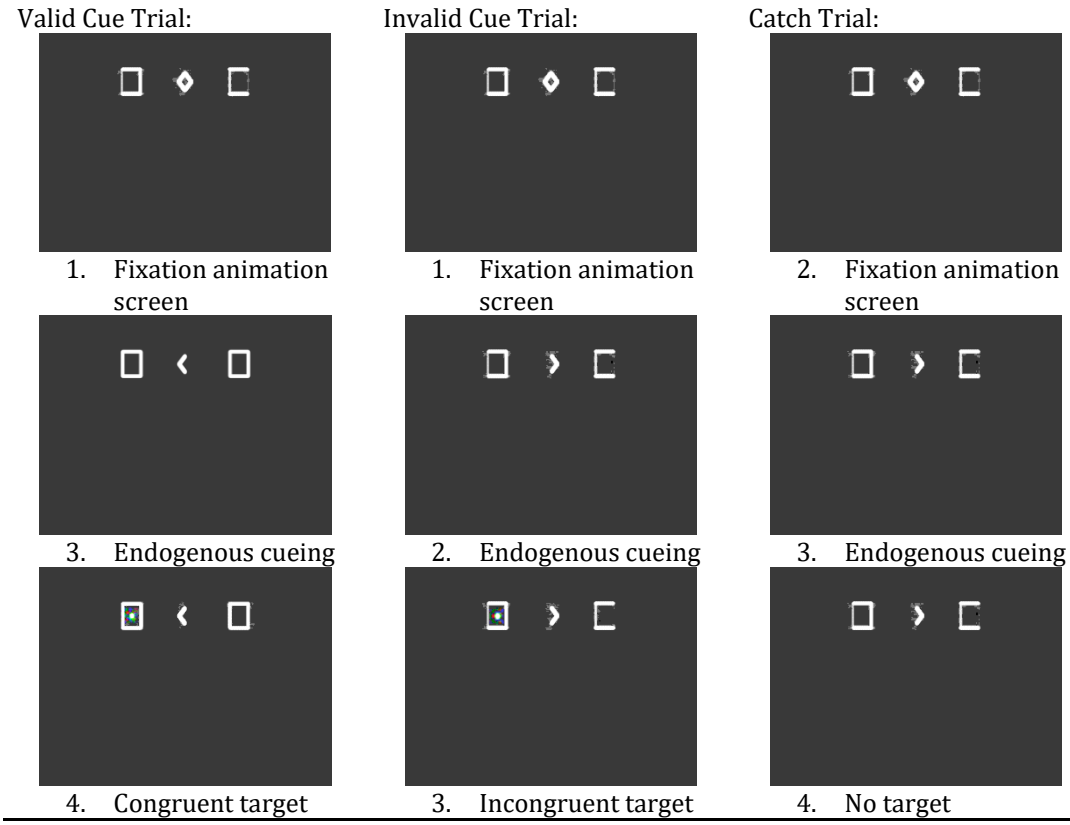


Figure 5.28: Posner Task: Example Stimuli

5.7.2 Analysis

Initial analyses were concerned with typifying control performance on this task, in order to serve as a point of comparison for patient behaviour. Table 5.11, below, details the data cleaning exercise conducted prior to analysis.

Dependent Variable	Exclusion Rule	Justification	No. of cases excluded (% of total trials)
RT	RT <200ms for target present trials when a response is recorded is coded as anticipatory. Anticipatory trials are then removed.	Visual inspection of the histograms revealed a clear bimodality with a local minimum of 200ms. Therefore, RTs of <200ms were coded as anticipatory responses and were excluded.	12 (0.02%)
Error rate: catch trials	If participants respond on >37.5% of catch trials (which is the lower cut off for chance responding), exclude this participant from analysis	If participants are responding to more than the 37.5% of trials, this indicates that they are not interacting with the task in a meaningful way as they are responding to trials when no stimulus is presented, thus their data cannot be analysed further	N/A

Table 5.11: Posner Task: Data Cleaning Exclusion Criteria

Patient 1 completed only one of the two experimental blocks as this patient failed to respond to any trial, causing all trials to be recorded as time-outs. The test was abandoned after the first block, as it was clear that this patient was unable to interact meaningfully with the task. Qualitative notes taken at the time of assessment for this patent refer to the patient as failing to look at the screen, focusing instead on the buttons despite prompting. Patient 4 completed only 7 trials, as this patient was unable to locate the computer screen in space, which was causing this patient undue anxiety. As such, the test was abandoned for this individual.

The endogenous Posner task measures voluntary shifts of attention. This can be quantified using the cueing effect (CFX), which is a measure of attention calculated from the RT cost of invalidly cued trials compared to validly cued trials. The CFX was calculated using the following formula:

$$CFX = median\ RT\ invalid\ trials - median\ RT\ valid\ trials$$

5.7.3 Results

In order to determine task adherence, data were initially screened in order to establish the false alarm rate (responding during catch trials when no target was presented), the anticipation rate (responding before a target was presented or within 200ms of a target), and the accuracy rate by target side (left and right) and cue validity (valid and invalid).

Controls demonstrated almost perfect task adherence, with no false alarms (save for one control who responded on 3.1% of catch trials). Patients were largely the same, with three notable exceptions, patient 2 (31.1% false alarms), patient 21 (12.5% false alarms), and patient 25 (21.9% false alarms). The rates observed for patients 2 and 25 were relatively high, but were not deemed so high as to warrant exclusion of their data as a consequence of task non-compliance. Control participants rarely made anticipatory responses, with the highest rate recorded as 0.6% of trials. Patients also demonstrated a low rate of anticipatory responding, with a range of 0-3.1% of trials recorded as anticipatory.

Controls performed perfectly on target-present trials, responding to all targets presented, with no main effect of target side or cue validity, nor any evidence of an interaction, $F(1, 17) = 1$, $p = 0.331$ for each of target side, cue validity, and side by validity interaction on mean accuracy. Note that one control missed 0.6% of invalidly cued right-sided trials. Overall, patients were less accurate than controls, however the detection rate was greater than 95% for all patients with some exceptions, detailed below.

Of the PCA patients, patient 1 and 4 failed to respond on any trial (note that patient 4 completed only 7 trials), patient 2 demonstrated a greater deficit for the detection of right-sided targets (see Figure 5.29). PCA patient 5 appeared

generally within normal limits, responding on fewer left-sided trials than right (88% and 98%, respectively). One other NDD patient (patient 7) demonstrated reduced response rates (responding to fewer left- than right-sided trials, 91% and 95% respectively). One aphasia patient, patient 16, also demonstrated a level of impairment, recording the same pattern as patient 7, with a response rate of 82% for left-sided trials and 95% for right-sided trials.

Controls generally demonstrated greater RTs for invalidly cued trials. Indeed, a main effect of cue validity was observed on median RT, $F(1, 17) = 26.192$, $p = 0.000$, with longer RTs for invalidly cued trials (mean valid: 402.13ms, mean invalid: 434.15ms). No main effect was observed for target side, $F(1, 17) = 3.850$, $p = 0.066$, and there was no significant interaction between cue validity and target side, $F(1, 17) = 0.005$, $p = 0.947$.

Figure 5.29, below, presents the CFX for controls and patients. Control CFX crosses zero, indicating that for some controls there is no cueing effect for either side. Generally, when a cueing effect was observed in controls it was seen to be equivalent across both sides, and positive, indicating a greater RT cost for invalidly cued trials.

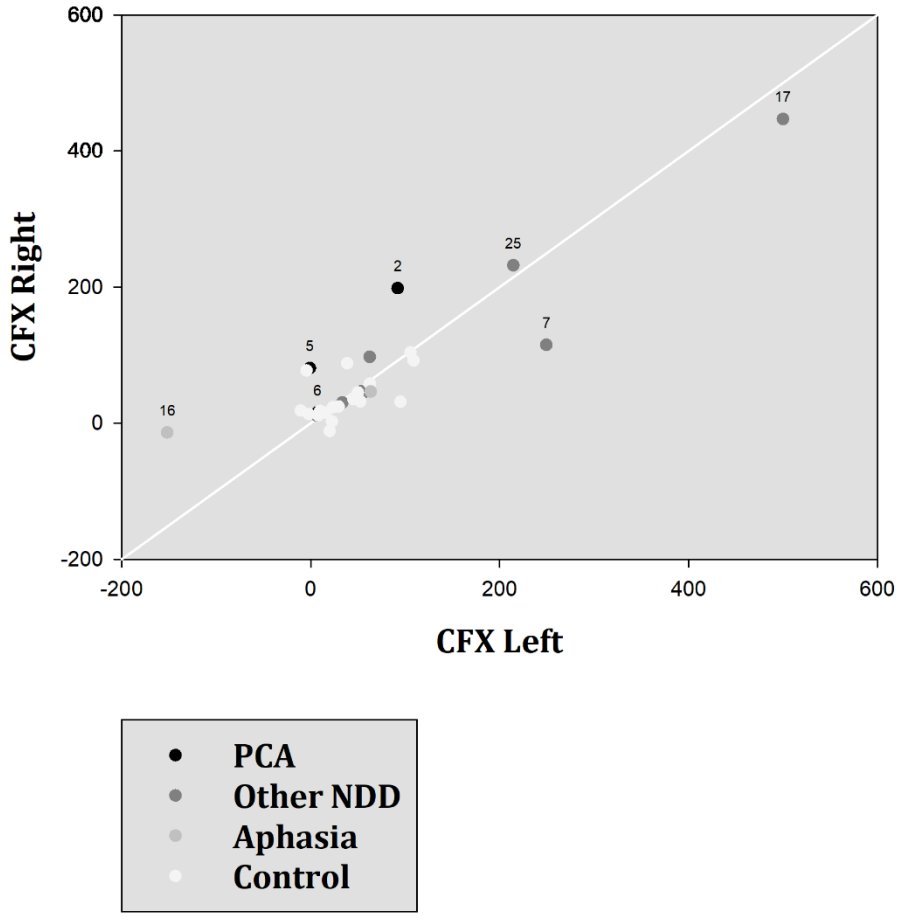


Figure 5.29: Scatterplot Lateralised CFX
Note: Solid white line on plot indicates line of origin.
Superscripted labels refer to patient number for all PCA patients (2, 5, 6) and anomalous performers.

PCA patients performed variably on lateralised CFX. Patients 5 and 6 had CFX scores equivalent to the control group, with no obvious laterality effects. PCA patient 2 demonstrated a general slowing of responses, similarly with a marginally larger CFX for right-sided targets over left.

There were a number of outlying cases from the other NDD group. Patients 7, 25, and 17 all demonstrated a general slowing of responses – without any laterality effects. It is possible that these magnified CFX scores may be the result of deficits in visual attentional orienting, observed variably in AD (Fernandez-Duque & Black, 2006). Patient 16 from the Aphasia group, however, presents a particularly complex case. This patient has a control-level CFX for right-sided targets, with a negative CFX for left-sided targets, implying a greater RT cost for

validly over invalidly cued left-sided targets. This patient was also observed to respond to fewer invalidly than validly cued left-sided targets (67% and 87%, respectively). This response rate to invalidly cued left-sided targets is close to the upper cut-off for chance responding (which is 62.5%), therefore the apparently anomalous CFX for left-sided targets may be the consequence of noise within the data as a result of non-responding. It is interesting to note, however, that this patient presented spontaneous right-sided neglect in the optic ataxia by confrontation task, therefore this patient may be exhibiting complex visual-attentional deficits which do not fit with any prior model of attentional orienting.

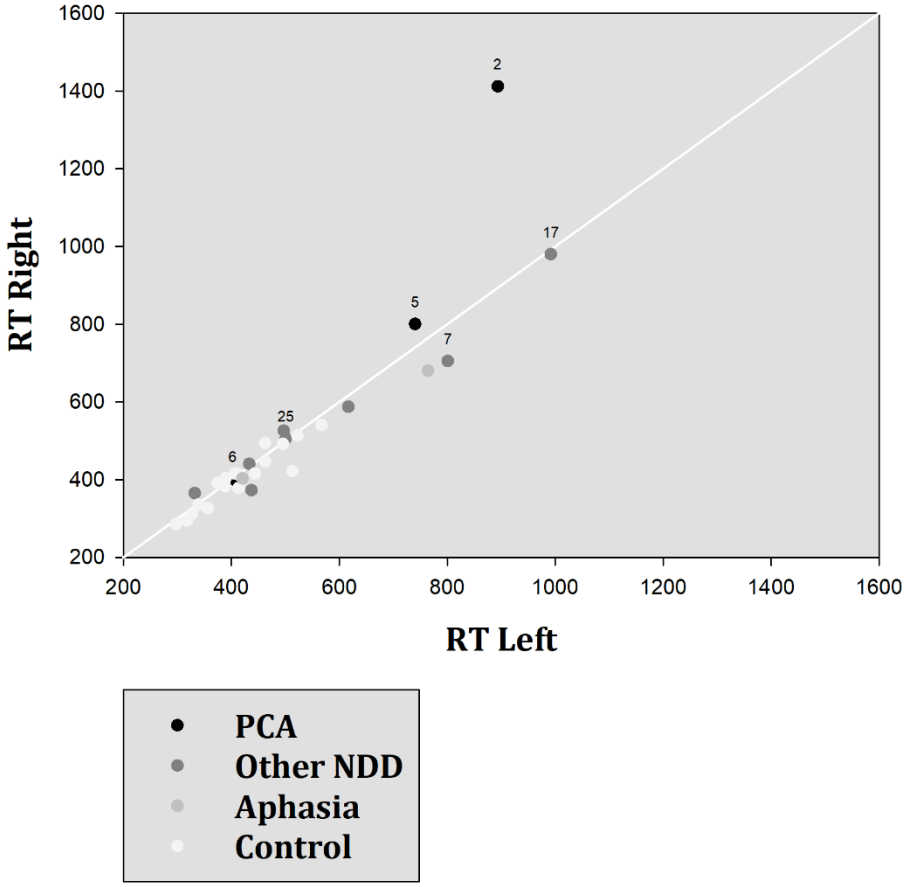


Figure 5.30: Scatterplot Lateralised Reaction Time
Note: Solid white line on plot indicates origin.
Superscripted labels refer to patient number for all PCA patients (2, 5, 6) and anomalous CFX performers.

Figure 5.30, above, presents mean RT data for left- and right-sided target trials for controls and patients. Note that the mean was calculated from the median RTs for valid and invalidly cued conditions for that target side. Controls typically show consistent RTs across each side. Other NDD patients 7, 16 and 17 have longer RTs than controls and other patients within their group, but none show any notable effect of side. These longer RTs are consistent with the greater CFX scores observed in Figure 5.29. Of the PCA patients, patient 6 performs at the level of control participants, exhibiting no effect of target side on median RT. Patient 5, similarly to the abnormally performing other NDD patients described above, shows longer RTs than controls but with no discernible effect of target side. Data from patient 2 demonstrate much greater response latencies for right-sided trials than left, consistent with the greater CFX observed for right-sided trials in Figure 5.29. This is a notable finding, as greater response latencies for right-sided trials over left are not readily explained by any typical visual-attentional deficits associated with PCA. Figure 5.31, below, presents response data from patient 2 in order to investigate this unusual pattern of behaviour more closely.

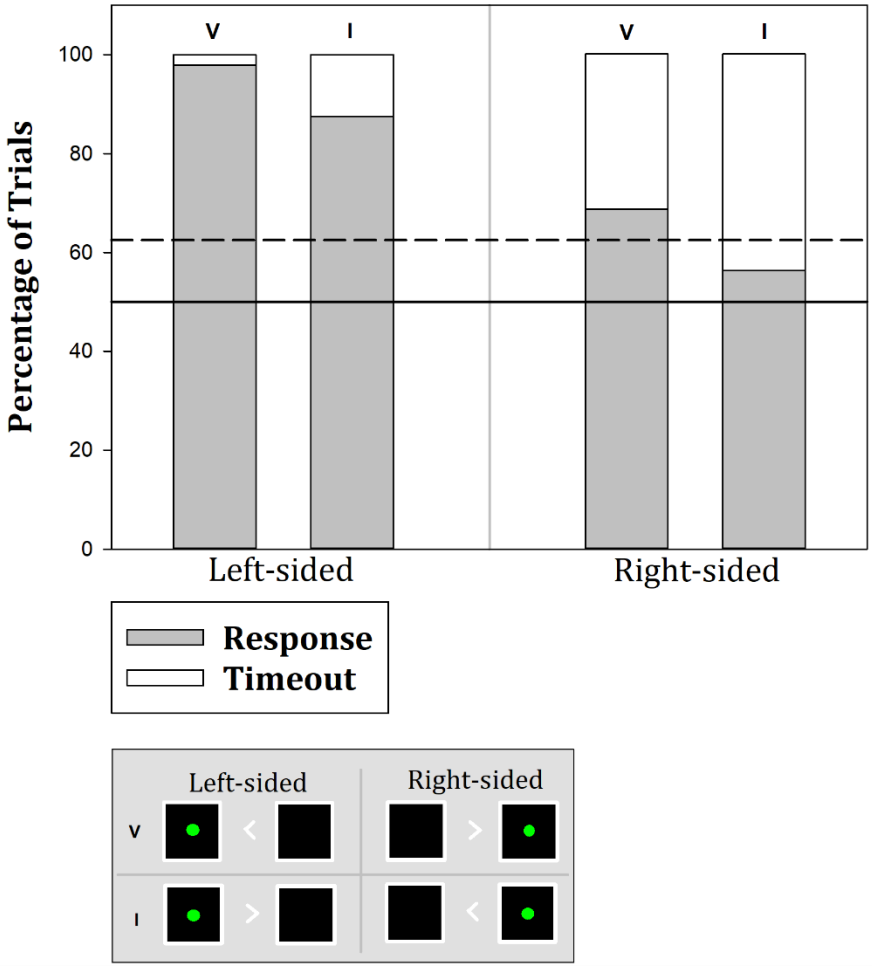


Figure 5.31: Response Frequencies Across Target Side and Cue Validity for Patient 2
Note: — represents chance (50%), **- - -** represents upper cut-off for chance responding (62.5%). V = valid cue, I = invalid cue.

Figure 5.31 indicates that patient 2 fails to respond to the target on more right-sided than left-sided trials, by a substantial margin. Indeed, this patient's response frequency is around chance level for right-cued trials (particularly for invalidly cued trials, which are within the limits of chance responding). Right-sided neglect, although not commonly reported (but, notably, more frequently observed in PCA patients than those with focal brain lesions), may explain this pattern of behaviour (Andrade et al., 2010). Right-sided neglect is often less severe on presentation than left-sided neglect, and is thought to require bilateral brain atrophy, with concomitant damage to the right hemisphere as well as the left (Andrade et al., 2010). Chapter 8 presents imaging data from this

patient which may support the hypothesis of this behaviour being linked to right-sided neglect. Alternative hypotheses for this pattern of behaviour are less readily supported. For example, simultanagnosia does not explain the apparent right-sided deficit observed for this patient as the frequency of timeouts would be approximately equal across all cue side and validity conditions, as there would be no target laterality nor cue validity effect on which targets were identified. An alternative explanation would be an undiagnosed hemianopia. However, in such a case, deficits associated with the hemianopia would be observed in the other experiments conducted with this individual (such as the line bisection and cancellation tasks). Right-sided visual neglect may also explain the chance-level responding observed for invalidly cued right-sided trials. This patient is observed to have a slight accuracy advantage on valid over invalidly cued right-sided trials, therefore it is reasonable to theorise that the patient is able to use the endogenous cue to the right on valid trials to orient their attention to the previously unattended space. In invalid trials, this patient is seldom able to search the unattended right side of space to find the target, perseverating their attention to the left following the invalid cue. Similarly, on invalidly cued left-sided trials, it may be the case that the patient begins to orient their attention towards to previously unattended right side of space, but can then track their attention back to the favoured left side in order to detect the target with a good level of accuracy. Further elaboration on the possible presentation of right-sided neglect observed in this patient, and the relation to models of visual attention are presented in the discussion section of this chapter.

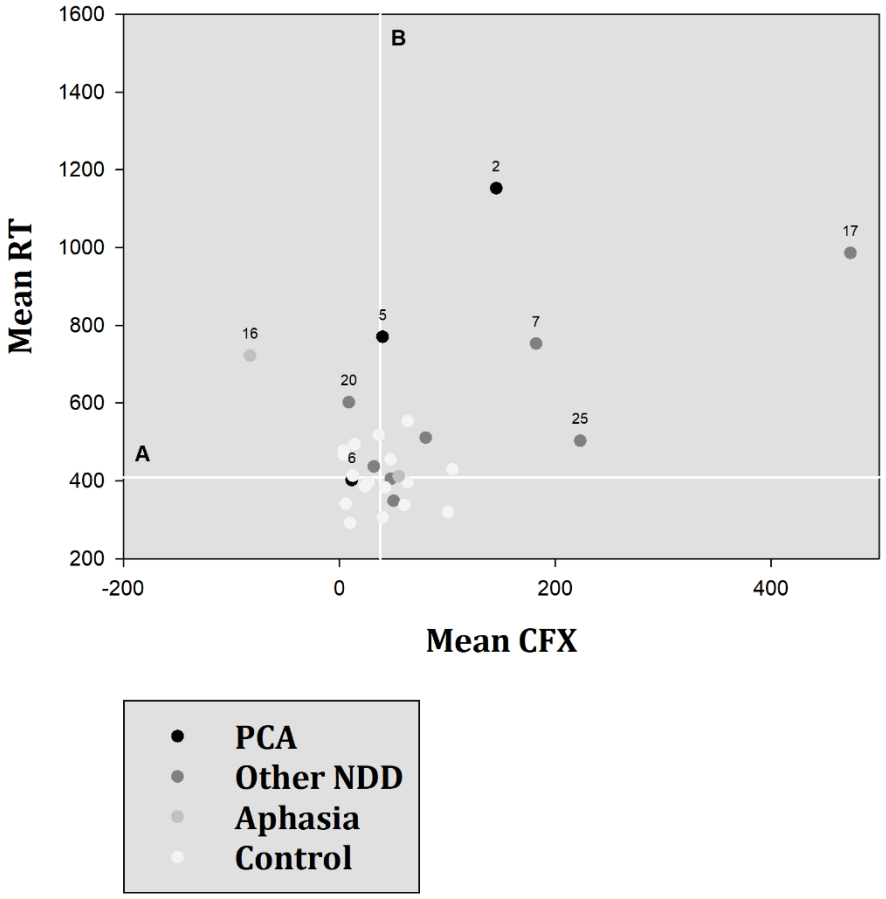


Figure 5.32: Scatterplot of Mean Reaction Time by Mean CFX
Solid white lines on plot indicates control mean A) RT and B) CFX
Superscripted labels refer to patient number for all PCA patients (2, 5, 6) and anomalous performers.

Figure 5.32 presents the grand mean RT plotted against the grand mean CFX for each control and patient. Responses which are close to the control CFX value (line B), but above the control RT (above line A) are those who exhibit slowed visual processing. This interpretation is based on the expectation that deficits in visual processing would manifest as increased RT latencies. Notable examples are PCA patient 5, as well as other NDD patients 7, 16 and 20. In contrast, those with a mean RT close to controls (line A), but a greater CFX value (rightward of line B) are individuals with slowed attentional shifting, for whom invalidity has a greater cost on speed of responding when compared to controls. Deficits in CFX (e.g. greater CFX values) are interpreted as representing slowed attentional shifting, as CFX is a measure of the cost of invalidly over validly cued trials.

Thus, a greater CFX value must represent a greater RT cost incurred from invalidly over validly cued trials, and therefore serves as a measure of the speed of attentional shifting. Other NDD patients 7, 17 and 25 present in this manner.

PCA patient 2 appears to demonstrate deficits in attentional processing – with a greatly magnified mean RT compared to all other patients within the sample – in addition to somewhat slowed visual attentional shifting, presenting with a larger CFX than either of the other PCA patients, and the majority of other NDD patients. This deficit in attentional shifting (specifically observed to be a deficit in shifting attention to the right) is further evidence of possible right-sided visual neglect. In contrast, PCA patient 5 appears to demonstrate deficits in visual processing (greater mean RT than almost all other patients within the sample), with the absence of associated slowness of visual attentional shifting (CFX around the level of controls). There was no evidence of any laterality effect for patient 5, implying that the deficits in attentional shifting may not be a consequence of visual neglect. Patient 6 performed at the level of controls.

5.8 Discussion

The primary aim of the series of experiments and assessments reported within this chapter was to gain a detailed phenotype of visuoattentional deficits associated with PCA. The secondary aim was to determine whether visuoattentional deficits are present in patients with diagnoses other than PCA.

Evidence of the core attentional symptoms assessed by the experiments reported within this chapter are summarized under headings, below.

5.8.1 Optic Ataxia

OA-like symptoms were observed in all of the PCA patients assessed in the OA by confrontation task, with misreaching errors in free vision worsening under fixation. OA has been considered a defining feature of PCA, and is listed as one of

the core cognitive symptoms in the recent classification framework by Crutch and colleagues (Meek, Shelton & Marotta, 2013; Crutch et al., 2017). Minor misreaching errors were common in non-PCA patients, but these did not constitute OA.

PCA patient 1 exhibited left-sided motor neglect and was therefore unable to use their left hand in either condition of the OA by confrontation assessment. However, interestingly, under fixation this patient would not initiate a movement with their right hand, reporting that "there's nothing there". These results are qualitatively similar to those found in an investigation by Meek and colleagues, in which PCA patient MTB was unable to initiate a movement in a peripheral grasping task under central fixation condition (Meek, Shelton & Marotta, 2013). The difference between the two patients, however, is that MTB maintained that she could see the stimuli, but that initiating a movement was "too difficult", whereas patient 1 in the present investigation claimed that they could not see the target. It is possible, therefore, that patient 1 was unable to detect the target in either the OA by confrontation task, or the extinction by confrontation task, as a consequence of a severely narrowed attentional window, a hemianopia, or possibly as a result of a degraded neural representation of the visual periphery (further elaboration later in this section). Additional qualitative insight from this patient on their visual experience is presented in Chapter 7.

A different PCA patient demonstrated magnetic misreaching under the fixation condition (patient 4) – always touching the point of fixation (the experimenter's nose), rather than reaching to the peripheral targets. This inability to decouple reach direction from gaze direction is considered a limb-dependent form of optic ataxia (Jackson, Newport, Mort & Husain, 2005). Magnetic misreaching has been described as a 'primitive' form of reaching (Milner, Dijkerman, McIntosh, Rossetti & Pisella, 2003). It has been hypothesized that the tendency to reach towards the point of fixation may be a hard-wired feature of cortical circuitry which is normally modulated – most likely by the superior parietal cortex –

therefore, lesions to this region cause the inhibitory control to be lost, leading to the subcortical-driven 'default' behaviour of magnetic misreaching (Milner et al., 2003). A similar pattern of behaviour was observed in a non-PCA patient (patient 16). This patient failed to use their right hand in any condition on the OA by confrontation task, despite being self-reported right handed, which is suggestive of spontaneous right-sided motor neglect (as this patient used their right hand in other tasks). This patient was unable to comply with the task instructions in the fixation condition, always looking at the target before reaching, rather than maintaining fixation. This lack of ability to decouple their locus of attention (determined by their eye movements) from their arm movement is suggestive of magnetic misreaching.

Perhaps the most striking observation from this experiment was that of spontaneous left-sided motor neglect observed in PCA patient 5 under fixation. The PPC (lesions to which result in OA) is known to be a multisensory region, located between the occipital (visual) and anterior parietal cortex (proprioceptive) (Blangero et al., 2007). Likewise, there is evidence that the PPC integrates motor information about the hand in order to plan the movement (Blangero et al., 2007; Medendorp, Goltz, Crawford & Vilis, 2005). OA, resulting from damage to this area, may therefore not be a purely sensory-motor or visuoattentional disorder, but rather a deficit of visuo-proprio-motor integration (Blangero et al., 2007). It is possible, therefore, that under the fixation condition – patient 5 did not have visual feedback of the hand, and therefore had to rely on proprioceptive information from that hand in order to complete a reach. Given that the patient failed to use the hand at all, it is additionally possible that they may have primary proprioceptive deficits, possibly as a consequence of atrophy to primary sensory cortex or areas representing the left hand and arm in space (the body schema), thus the spontaneous underuse of this hand may be the consequence of a deteriorated representation, manifesting behaviourally as spontaneous underuse in the more computationally taxing condition of no visual feedback.

The classic characterisation of OA as a dorsal stream disorder following lesions to the PPC, dissociated with the object identification (ventral stream) deficit of visual agnosia, resulting from lesions to the occipito-temporal cortex, has led to the dogmatic view that pure OA is a condition with no associated perceptual deficits (Pisella, Rossetti & Rode, 2017). However, evidence from the PCA patients within the present sample suggests that misreaching deficits can and do co-occur with perceptual and attentional deficits, and similarly, functional neuroimaging data has revealed systematic activation within the PPC in all perception tasks performed without a motor response, evidencing a major role of the PPC in attentional phenomena (Pisella et al., 2017). Additionally, there is evidence that the PPC is implicated in compensating for the under-representation of peripheral vision which accompanies the central magnification (occurring as a consequence of the high level of receptor density and small receptive fields in foveal vision) (Vindras et al., 2016; Pisella, 2017). Thus, OA misreaches as a result of damage to the PPC may be highly informative, and reveal what hand movement accuracy and precision would be if the human motor system did not include specified corrective processes for reaching to non-foveated targets (Vindras et al., 2016). This line of research provides further evidence for the PPC as an integrative, multisensory system, evidently concerned with both perceptual and attentional processes. Similarly, evidence from grasping tasks which indicate a failure to scale the hand appropriately when grasping (a further impairment related to OA), as well as online-reach-correction tasks suggests that the deficits observed in OA relate to both visuomotor and perceptual processes (Milner, Dijkerman, McIntosh, Rossetti & Pisella, 2003; McIntosh, Mulroue, Blangero, Pisella & Rossetti, 2011). Further elaboration on grip scaling in OA is presented in Chapter 6.

5.8.2 Extinction and Visual Neglect

Deficits on the extinction by confrontation task were only observed in PCA patients. No other patients were impaired on this task. Two of the PCA patients (patients 1 and 4) were too impaired to do the task, claiming to be unable to see

the stimuli. This impairment for peripheral visual stimuli has been reported in prior investigations of PCA, in which reduced cortical representations of the peripheral visual fields were observed using an fMRI paradigm (Shames, Raz & Levin, 2015). This compromised peripheral visual representation was linked to dorsal parieto-occipital damage, specifically to the dorsomedial area (V6), located in the parieto-occipital sulcus and found to contain a large representation of the visual periphery (Shames et al., 2015). It is also possible that the inability of patients 1 and 6 to detect the peripheral stimuli may have been a consequence of a hemianopia or narrowed attentional window (simultanagnosia).

Left-sided extinction was strikingly observed in patient 5 (who only identified the right target under bilateral stimulation) and additionally observed in patient 2. In both cases, the visual extinction meets previously specified limits for 'severe', as more than 60% of contralateral stimuli were omitted (Gainotti, D'Erme & Bartolomeo, 1991; Andrade et al., 2010). Patient 5 was also observed to present with spontaneous left-sided motor neglect in the OA by confrontation examination (discussed above), as well as a rightward bias in the invisible cancellation task, which suggests that a left-sided neglect manifests under certain task demands for this individual.

The line and gap bisection task revealed interesting general results, namely that no advantage was observed for EWS and EWB over the more common dependent measure of DBE for identifying PCA-like deficits on this task. In fact, none of these measures accurately captured or characterised the interesting behaviours observed from patients on this task, such as the extreme responses observed from one PCA patient (patient 4), who presented with left-sided neglect on the line bisection, but extreme simultanagnosia or possibly very severe left-sided neglect on the gap bisection task (only ever responding by pressing the rightmost stimulus). The most informative characterisation of the behaviours of the PCA patients therefore came from inspection of the actual raw trial responses, rather than the summary measures. Patient 4, as an example,

illustrates the surprising usefulness of the gap bisection task at revealing visuoattentional deficits over the more conventional line bisection task. Thus, the line and gap bisection tasks appear to require different cognitive processes, or perhaps have different visuoattentional demands. This assertion was further supported by the results of two non-PCA patients. Patient 21 appeared insensitive to the changing endpoints of the stimuli on the line bisection, but accurate to the endpoints on the gap bisection task, whereas patient 12 showed an almost inverted pattern - with accurate responses on the line bisection task, but responses either in the true centre, or on either endpoint in the gap bisection task. Half of the PCA patients were impaired on this task (with responses such that the EWB and EWS were rendered meaningless, despite the interesting behavioural patterns which were possible to observe from the raw responses). The majority of non-PCA patients were unimpaired on this task, with the exception of patient 21 (mentioned above) who appeared to show some visuoattentional deficits on the line but not gap bisection, one in whom the opposite pattern was true (patient 12), and one in which executive dysfunction was suspected on account of their seemingly random responses (patient 16).

The Posner task revealed a strange deficit in one PCA patient, where the patient was impaired in the detection of right-sided targets, regardless of cue validity (patient 2). These results may suggest a mild right-sided neglect. Further inspection of this patient's raw responses on the gap (but not line) bisection task imply a slight leftward bias, which may be consistent with right-sided neglect.

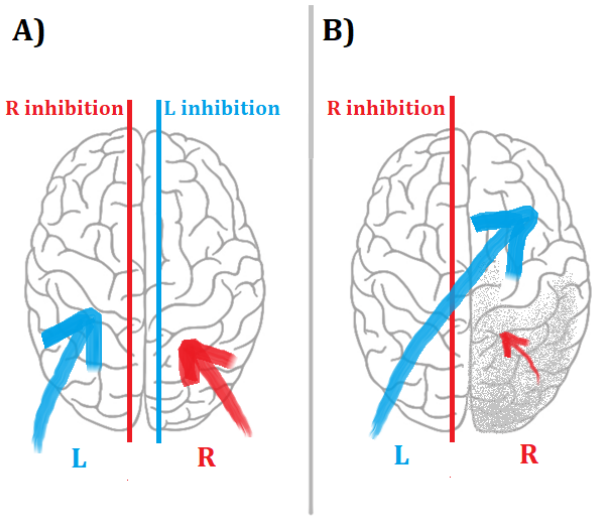


Figure 5.33: The Opponent Processor Model of Visual Neglect (Kinsbourne, 1970)
Key: A = healthy brain, B = right hemisphere damage, L = left hemisphere, R = right hemisphere. Coloured arrows represent the attentional vector from each hemisphere.

The opponent processor model of visual neglect, originally proposed by Kinsbourne (1970), posits that each hemisphere shifts attention towards the contralateral hemispace by inhibiting the other hemispace (Figure 5.33). The model further suggests that the healthy brain has a stronger rightward than leftward attentional vector (Kinsbourne, 1970). Therefore, damage to the right hemisphere leads to the disinhibition of the strong, rightward attentional vector from the left hemisphere, leading to the presentation of left visual neglect (Kinsbourne, 1970). According to this model, presentations of left-sided neglect would be worse than right-sided neglect due to the fact that the rightward attentional vector is stronger than the leftward in the healthy brain, therefore damage to the left hemisphere would produce only subtle right-sided neglect.

An alternative model of visual neglect, proposed by Heilman and Van Den Abel a decade later, suggested that the left hemisphere attends to contralateral space, whereas the right hemisphere attends to both contralateral and ipsilateral space (Heilman & Van Den Abel, 1980) (Figure 5.34). Therefore, following right hemisphere damage, attention is biased towards the right because the right hemisphere is no longer attending to the left, and the left hemisphere can only attend to the right (Heilman & Van Den Abel, 1980). Similarly, this model also

accounts for the far less severe presentation of right-sided neglect, as damage to the left hemisphere would result in reduced rather than absent attention to the right side (Bartolomeo & Chokron, 1999; Heilman & Van Den Abel, 1980).

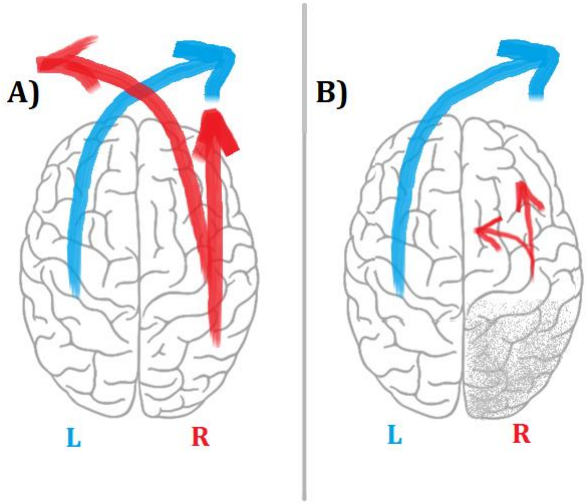


Figure 5.34: The Right Hemisphere Dominance Model of Visual Neglect (Heilman & Can Den Abell, 1980).
Key: A = healthy brain, B = right hemisphere damage, L = left hemisphere, R = right hemisphere. Coloured arrows represent the attentional vector from each hemisphere.

It is not possible to draw firm conclusions as to which model of visual neglect would fit with the presentation of apparent right-sided neglect observed from patient 2, and literature on right-sided neglect is scarce. There is evidence, however, that right-sided neglect occurs more frequently in PCA patients than in those with focal brain lesions (Andrade et al., 2010). It is also possible that behaviours associated with right-sided visual neglect may often be misattributed as naming or visual errors (Kleinman et al., 2007). A typical example would be the tendency for right neglect dyslexic patients to correctly retain the early letters of a word, but then to incorrectly substitute characters later in the word (thus 'purpose' is read as 'purple') (Berndt, Haendiges & Mitchum, 2005). There is some evidence that right-sided neglect may be task-specific (Lecours et al., 1987). Therefore, further research is necessary to develop tests to detect right-sided neglect, as traditional tests such as line bisection and cancellation tasks may not be sufficiently sensitive to detect it.

The cancellation tasks (visible and invisible) were included as a test for visual neglect. Indeed, these tasks were found to be very sensitive to deficits associated with PCA, with all PCA patients performing worse than non-PCA patients and controls on every measure. All non-PCA patients were additionally worse than controls, except on the measures of median *x* co-ordinate and number of target touches. Interestingly, the most sensitive dependent measure in detecting PCA was found to be median *x* co-ordinate (perhaps unsurprising, given the preponderance for visual neglect within this population), and total time. The invisible cancellation task was particularly revealing of deficits, as all PCA patients were impaired on the measure of total time.

All PCA patients continued searching until timeout on the invisible cancellation task, which implies that these patients were not sure whether they had touched each item, thus continued to respond to the stimuli until the experiment timed out. Impaired non-lateralised spatial working memory (SWM) has been hypothesized as a component which contributes to the presentation of visual neglect, as patients have difficulties in keeping track of spatial locations (Toba et al., 2018). Impairments in SWM would therefore cause patients to revisit targets which had previously been visited, particularly in tasks where no visual feedback is provided once targets had been touched (Toba et al., 2018). Consistent with this hypothesis, the neglect was observed to worsen for all PCA patients on the invisible cancellation task, with all patients' median *x* co-ordinate being rightward of the true centre of the screen. Thus, the cancellation tasks were revealing of both neglect in the PCA patients and a deficit of SWM – evidenced both by the increased rightward bias observed in the invisible task, as well as the consistent timeouts seen in all of the PCA patients.

5.8.3 Simultanagnosia

Perhaps surprisingly, an insensitivity to distractor number was observed for PCA patients on the pop-out visual search task – suggesting that these patients did experience the pop-out effects of the target. It was hypothesized that

patients with simultanagnosia would be observed to approach the pop-out task with a serial search strategy in order to compensate for their reduced visual attentional window. Two of the PCA patients presented with an abnormally high median number of saccades compared with controls, which may suggest that these patients were indeed applying a serial search strategy as a consequence of a reduced visual attentional window. Two non-PCA patients also presented with abnormally high median numbers of saccades on the pop-out task. However, the majority of non-PCA patients were within control limits.

On the conjunction visual search task, no effect of target eccentricity was observed for any patients. This is very surprising given that eccentricity effects are a well-documented feature of visual search tasks (Wolfe, O'Neill & Bennett, 1998). There was an effect of distractor number on median number of saccades (more saccades made with increasing number of distractors) for PCA patients and around half of the non-PCA patients, however, there was no effect of distractor number on median RT for PCA patients (or non-PCA), which suggests that their visual search was as fast as controls. More in line with the present literature on eye movement characteristics in PCA was the observation of shorter amplitude saccades compared with controls and non-PCA patients on the conjunction task (Shakespeare et al., 2015; Beh et al., 2015; Crutch, Yong & Shakespeare, 2016).

It is possible that the stimulus density was too low to elicit effects of eccentricity, and indeed to highlight effects of spatial neglect or simultanagnosia. The maximum number of items on screen was 17, and the on-screen stimuli were relatively small. Thus, perhaps this task was not attentionally demanding enough to be sensitive to visual attentional symptoms. Indeed, the observation that increasing number of distractors did not affect RT on the conjunction task suggests that the features were possible to process 'pre-attentively', thus using very little of the available attentional resource (Joseph, Chun & Nakayama, 1997).

It was not possible to assess for simultanagnosic local precedence effects on the Navon task since the PCA patients were all too impaired to proceed beyond the test condition. Similarly, it was therefore not possible to test the hypothesis as to whether the local form can 'become global' in the relief condition. However, there is an early indication that the relief condition may be a potentially useful measure of local interference, with generally greater RTs observed for identifying the relief letter compared to the global letter form.

The fact that all PCA patients (including patient 6, who had appeared relatively unimpaired on other assessments included within this battery) were too impaired to proceed to the experimental conditions on the Navon task suggests that the visuoattentional processing required was too great. Notably, two of the patients could not identify the letter forms, both saying they saw black squares and triangles. That they both reported seeing the same thing suggests a common deficit in processing these letter forms. Both of these patients made small errors on prior tasks of letter identification and reading (such as the BORB non-overlapping and overlapping letters task and alexia task, reported in Chapter 4). The errors on the letter identification task were qualitatively noted to be substitutions of morphologically similar letters (such as V for W, G for C, and I for L), but neither patient showed consistency in these errors. It is possible that the degradation of letter form recognition in the Navon task was a consequence of a type of visual crowding: although notably this is normally observed for peripheral rather than foveal targets (Crutch & Warrington, 2010). Perhaps more likely is that the deficits observed were due to features of the letters being incorrectly parsed into new elements. Figure 5.35, below, presents a hypothesized vision of the black squares and triangles which patients may be identifying when inspecting the figures.

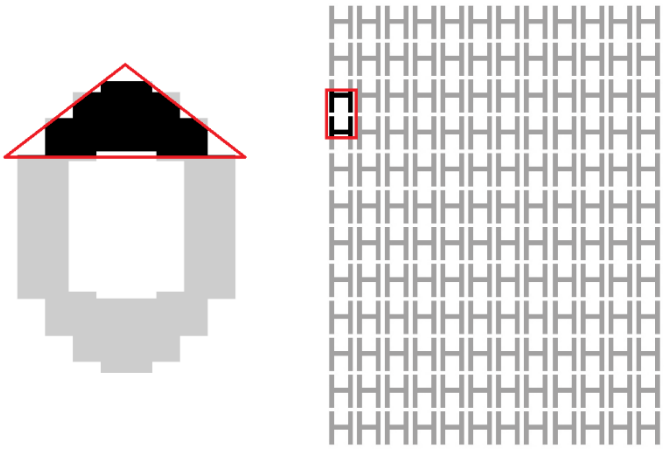


Figure 5.35: Misattribution of Shape in Navon Test Letters
Highlighted in red are the hypothesized areas where the black triangle (left) and black squares (right) may have been identified.

Without asking patients to identify specifically where on-screen the black squares and triangles were, Figure 5.35 merely presents a 'best guess'. Based on the 'best guess' hypothesis, it may be the case that a breakdown in Gestalt feature integration processing has occurred for these patients. The block-like nature of the large O, for example, may have caused these patients to incorrectly separate it into individual elements, and the close proximity of the small H's may have made the inter-stimuli spacing difficult to perceive. There is evidence that object processing can be impaired in simultanagnosic patients both for single and multiple objects, as a consequence of impaired dorsal-stream mediated Gestalt processing, particularly when the single objects are large (Rennig & Karnath, 2016). Thus, it seems reasonable to hypothesise that the failure to correctly identify the letters observed in two of the PCA patients (patient 2 and 6) was a consequence of disrupted Gestalt processing abilities, related to simultanagnosia (Zaretskaya, Anstis & Bartels, 2013).

5.8.4 Endogenous Orienting of Attention

All patients were less accurate than controls at target detection, although the majority of patients had a detection accuracy rate of over 95%. A small number of non-PCA patients demonstrated impairments in attentional shifting (patients 7, 16 and 20) as well as some who had slowed attentional processing (patients

7, 17, and 25). The majority of non-PCA patients therefore performed at the level of controls.

PCA patient 1 and 4 failed to detect any targets (patient 4 could not locate the computer monitor in space, therefore the task was abandoned after very few trials). Two of the three remaining PCA patients demonstrated abnormalities of visual attentional orienting and speed of attentional processing. One patient (patient 2, discussed above) demonstrated a particular deficit for the detection of right-sided targets, regardless of cue validity - with poor target detection rates for this side, as well as magnified response latencies. This patient thus showed a deficit in both shifting of visual attention as well as slowed attentional processing. PCA patient 5, in contrast, showed slowed attentional shifting with no associated deficit in attentional processing speed. This patient was therefore impaired in disengaging and subsequently re-engaging their attention following an invalid cue, but there was no effect of laterality. Therefore, this was not indicative of a neglect-driven disengage deficit. There is evidence that OA patients have deficits in shifting their attention to peripheral targets, or within their ataxic visual field, so the deficits in attentional shifting observed in the two PCA patients reported above may be, at least in part, a consequence of OA (Striemer et al., 2007; Striemer et al., 2008).

5.8.5 Future Directions for Research

The non-PCA patients all demonstrated relatively intact visuoattentional abilities, with only minimal examples of abnormalities within the group. The PCA patient group, however, were far more heterogeneous in presentation, with patients 1 and 4 appearing to be the most impaired, patient 6 appearing relatively unimpaired, and patients 2 and 5 falling somewhere in the middle. The invisible cancellation task was the only task in which a very high sensitivity and specificity to PCA could be gained, particularly relevant given the diverse spectrum of visuoattentional impairment observed within this patient group. The measure of total time taken – which can be interpreted as a measure of

visuospatial working memory – was particularly specific to PCA. Indeed, a recent review presented evidence to affirm that visual perception is dependent on visuospatial working memory (which in turn is associated with the posterior parietal cortex) (Pisella, 2017). It is possible, therefore, that deficits in visuospatial working memory may serve as an early indicator of degeneration in this region, and thus be a valuable avenue for future research for the development of effective screening tools for PCA (Perrochon, Kemoun, Dugué & Berthoz, 2014; Funayama, Nakagawa & Sunagawa, 2015).

Similarly, there was some evidence of possible (task specific) right-sided neglect in one PCA patient. Right-sided neglect may be more common than previously attested within the literature. Given that neglect is one of the cardinal symptoms of PCA (assuming it is captured within the 'space perception deficit' named by Crutch and colleagues as one of the cognitive features of PCA), future researchers should be mindful of the possibility of subtle signs of right neglect in PCA patients (Crutch et al., 2017). There appears to be a systematic bias within the literature towards diagnosing patients with PCA who present with right-hemisphere-related deficits (e.g. left-sided neglect) (Ryan et al., 2014). This concerning phenomenon further highlights the need for more targeted research into developing effective screening tools for left-sided presentations of PCA.

6. Experimental Chapter: Visuomotor Control

6.0 Introduction

6.0.1 Visuomotor Deficits in Neurodegenerative Disease

Visuomotor deficits in reaching for objects under visual guidance are typically associated with presentations of PCA, in tandem with deficits of visuoattentional and visuoperceptual abilities (discussed in Chapters 4 and 5) (Crutch, Yong & Shakespeare 2016; Meek, Shelton & Marotta, 2013). A visuomotor symptom canonically associated with PCA, as identified by a recent formal classification framework developed by Crutch and colleagues, is optic ataxia (OA) (Crutch et al., 2017).

OA, a component of Bálint's syndrome, has been described as a "defining symptom" of PCA and is often reported in case studies of PCA patients (Meek et al., 2013, p.1; Crutch et al., 2017). Patients with OA demonstrate deficits in visually-guided, goal-directed reaching and grasping movements, particularly in their visual periphery, despite having intact visual acuity, primary motor and sensory systems, and no associated visual field deficits (Meek et al., 2013). OA is associated with damage to the posterior parietal cortex (PPC), specifically the superior parietal lobe (SPL) and intraparietal sulcus (IPS) (Milner et al., 2001; Perenin & Vighetto, 1988; Striemer et al., 2009). The precuneus (which forms part of the SPL and is a crucial region in the dorsal visual pathway) is a particularly poorly understood brain region, residing in "one of the less accurately mapped areas of the whole cortical surface" (Cavanna & Trimble, 2006, p.564). Despite the relative paucity of research identifying the cognitive correlates of this region, lesion studies have identified it as a crucial region for the dorsal stream of human visual processing, and it is strongly implicated in presentations of OA, and thus appears critical to the control of visually-guided action (Cavanna & Trimble, 2006; Karnath & Perenin, 2005). Figure 6.1, below,

presents anatomical maps of the brain regions implicated in OA: the SPL and IPS (image A), and the precuneus (image B).

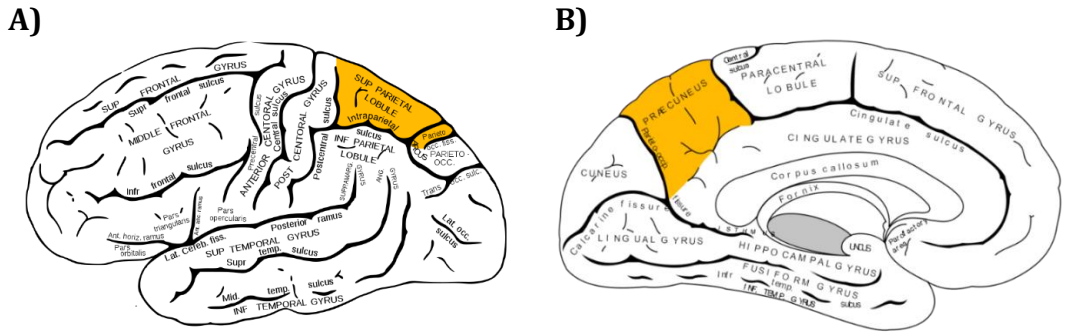


Figure 6.1: Brain Regions Implicated in OA
A) The superior parietal lobe (SPL) and intraparietal sulcus, seen here on the lateral face of the left cerebral hemisphere and B) the precuneus, forming part of the SPL within the medial face of the parietal lobe, seen here within the medial surface of the left cerebral hemisphere.

OA presents as misreaching in the contralesional visual field or with the contralesional hand, deficits in appropriately preshaping the hand for grasping, inabilities to correct movements 'on-line' once initiated, and abolished implicit avoidance of obstacles (Andersen, Andersen, Hwang & Hauschild, 2014; Schindler et al., 2004; Pisella et al., 2000; Perenin & Vighetto, 1988). Chapters 5 and 10 present more detailed accounts of signs, symptoms and theories relevant to OA.

OA is rarely screened for by clinicians in practice and seldom reported within the literature. Indeed, when screening for OA is reported there is little consistency in reporting of the methods applied (Borchers, Müller, Synofzik & Himmelbach, 2013). Screening for OA is uncommon, most likely because reporting of OA-like symptoms by patients is rare, except in cases when symptoms are very severe. Indeed, symptoms of OA have been described as 'covert' and thus, are usually only identified by targeted, highly specific assessments (Vighetto & Krolak-Salmon, 2013). OA is most likely a covert symptom because behavioural adaptations to overcome OA-related impairments are easy to adopt. For example, looking at an object before reaching for it will dramatically reduce or even eradicate the errors in reaching,

observed in OA. Thus, OA is unlikely to affect the quality of life of patients, or their activities of daily living, except in the most extreme cases. Therefore, OA may often fall beneath the 'clinical radar' at consultation.

OA is usually reported in the context of Bálint's syndrome, which occurs as a result of bipareital damage. In the context of neurodegenerative disease, Bálint's syndrome (and specifically OA) is strongly associated with PCA (Crutch et al., 2017). OA occurring in isolation, usually as a result of unilateral lesions to the superior parietal lobe and intraparietal sulcus, has been coined "pure" OA (Garcin, Rondot & de Recondo, 1967; Perenin & Vighetto, 1988; Striemer et al., 2009). OA has not, at the time of writing, been observed in typical AD.

6.0.2 Justification for Tests of Visuomotor Control

The tasks presented within this chapter were included in order to assess different components of the typical presentation of OA - misreaching, 'mis-scaling', and 'mis-avoiding'. It should be noted, however, that the current diagnostic criteria for OA dictates that the individual should not demonstrate any additional deficits in vision, attention, or proprioception (Meek et al., 2013; Borchers, Müller. Synofzik & Himmelbach, 2013; Bálint & Harvey, 1995). The patients investigated herein are not universally free from such deficits, therefore inferences of OA-like symptoms drawn from these results must be interpreted with due caution.

Deficits in reaching to targets, particularly those peripheral from fixation, are perhaps the most characteristic feature of OA (Andersen, Andersen, Hwang & Hauschild, 2014; Blangero et al., 2007; Buxbaum & Coslett, 1997; Striemer et al., 2009). OA pointing errors are typically hypometric (towards fixation) for eccentric targets, and hypermetric (away from fixation) for targets closest to fixation (Rossetti et al., 2005; Milner, Dijkerman, McIntosh, Rossetti & Pisella, 2003). The most extreme presentations of OA may result in errors whereby the patient responds only to the point of fixation, resulting in 'magnetic

misreaching' (Carey, Coleman & Della Sala, 1997). Chapter 9 presents a detailed overview of the typical misreaching errors observed in OA. In the interests of brevity, these details will not be repeated within the present chapter.

OA misreaching is typically assessed using the confrontation method, which is an inherently subjective measure (Borchers, Müller. Synofzik & Himmelbach, 2013). The pointing task reported within the present chapter attempts to measure OA-like misreaching by using a touchscreen task to record pointing errors to targets presented at different degrees of retinal eccentricity. The task was developed and programmed for the present investigation. No prior literature available at the time of writing reports the use of computerized pointing tasks in the assessment of patients with PCA.

In neurologically normal individuals, adjustment of the aperture of the index finger and thumb prior to grasping an object (the peak of which is referred to as the 'maximum grip aperture' (MGA)) is linearly related to object size (Jeannerod & Decety, 1990; Jeannerod, Arbib, Rizzolatti & Sakata, 1995; Milner, Dijkerman, McIntosh, Rossetti & Pisella, 2003). In contrast, OA patients typically show impairments in grip scaling, whereby they will not accurately or appropriately pre-shape their hand prior to grasping an object (Whitwell, Striemer, Nicolle & Goodale, 2011). OA patients are typically unimpaired in perceptual matching tasks, where the size of the object is estimated using the thumb and index finger, and no grasp is executed (Milner et al., 2001). In contrast, visual form agnosic patients typically show the opposite pattern (Whitwell, Striemer, Nicolle & Goodale, 2011). This divergence in behaviour between OA and visual agnosia has been cited in support of a double dissociation between the dorsal and ventral streams of visual processing (Milner & Goodale, 1995; Whitwell et al, 2011).

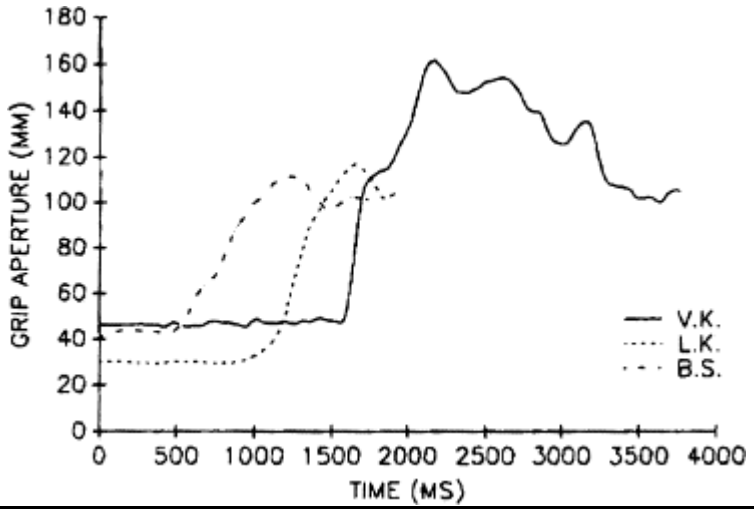


Figure 6.2: Typical MGA for OA Patient VK (from Jakobsone, Archibald, Carey & Goodale, 1991)
Note: LK and BS are two representative control participants.

Figure 6.2, above, presents MGA results from an OA patient (VK) in comparison to two healthy controls. Research in human prehension typically draws a distinction between two separate components of the prehension movement; the first 'transport' component in which the arm moves towards the target (often equated to an aiming movement), and the second 'grasp formation' component (Jakobsone, Archibald, Carey & Goodale, 1991). The abnormalities in prehension observed from OA patients are in the later 'grasp formation' phase where, rather than smoothly finishing the grasp movement following one MGA peak (as can be observed from the control data presented in Figure 6.2), OA patients typically have several secondary MGA peaks in their movement profile, with an MGA that does not have close correlation to the object size – as would be observed for controls (Jakobsone et al., 1991; Glover, 2003).

Similarly to pointing performance, grasping performance is observed to 'improve' under delayed conditions for OA patients (Milner et al., 2001). This improvement is typically related to the stronger correlation between MGA and object size observed in the delayed, rather than immediate, grasping conditions (Milner et al., 2001). As with pointing tasks, this is generally hypothesized to be as a consequence of the use of perceptual visual short-term memory for the delayed task (a ventral stream function), rather than on-line dorsal stream

processing (Milner et al., 2001; Milner, Dijkerman, McIntosh, Rossetti & Pisella, 2003; Milner & Goodale, 1995).

PCA patients have been observed to demonstrate results similar to OA patients on grasping tasks in one investigation by Meek and colleagues, with a lack of grip scaling and protracted movement durations observed under immediate reaching conditions (Meek, Shelton & Marotta, 2013). Interestingly, this study revealed perceptual deficits in the PCA patients, whereby grip scaling was impaired in a matching task (Meek et al., 2013). In addition, there was no 'improvement' for PCA patients for a grasp following a delay, as has been observed for OA patients (Meek et al., 2013). It is likely, therefore, that the PCA patients studied within the sample had rather more diffuse damage than in typical OA, resulting in impairments in ventral stream functions (like perceptual matching and visual short-term memory) which may generally be spared in 'pure' OA (Meek et al., 2013). A prior investigation by the same researchers found a different pattern of deficits in a sample of three PCA patients, with impaired matching and delayed grasping, but preserved grip scaling in the immediate grasping condition (Meek, Desanghere & Marotta, 2010). The authors proposed that the pattern of behaviour observed may reflect a 'ventral' variant of PCA (Meek et al., 2010).

In the present study a grasping and perceptual matching task were presented to patients in order to assess the presence of OA-like grip scaling anomalies. In OA, the predicted pattern would therefore be a reduced or absent MGA to object size correlation (an absence of grip scaling), but a better correlation between MGA and object size in the perceptual matching condition, indicative of preserved perceptual abilities.

Reach trajectories in neurologically normal individuals are influenced by surrounding objects, such that the reach will avoid any potential obstacles (Schindler et al., 2004). The brain protects the body against potential collisions using an in-built tendency to veer away from non-target obstacles, even when

they are too far away to be likely to cause a collision (Schindler et al., 2004; Tresilian, 1998). This obstacle avoidance system has been demonstrated to be part of the dorsal stream of visual processing, with imaging and neurophysiological studies identifying the neural correlates of this behaviour as the superior areas of the posterior parietal cortex, specifically the IPS (Schindler et al., 2004). This assertion was further supported by evidence from visual form agnosic patient DF (who has bilateral ventral stream damage), in whom intact obstacle avoidance was observed, suggesting that DF may depend on intact dorsal stream functions in order to navigate between the obstacles successfully (Schindler et al., 2004). However, recent evidence of OA-like misreaching in DF suggests that her dorsal stream is not intact, as previously attested (Rossit et al., 2018; Hesse, Ball & Schenk, 2012, 2014). Neglect patients have been observed to account for obstacles in either side of space effectively (when reaches are performed to a point beyond the obstacles), however, when these patients were asked to point to the midpoint between the obstacles they failed to account for the obstacle on the left (neglected) side of space (McIntosh, McClements, Dijkerman, Birchall & Milner, 2004).

Obstacle avoidance performance is typically assessed using a board with removable cylindrical 'obstacles' (dowels), which can be positioned at different lateral distances from the true midpoint in order to manipulate how close these obstacles are to the idealised, central hand trajectory. A task of this design was used in order to assess obstacle avoidance behaviour in the patients within the present sample.

Evidence from patients with OA formed the basis for the assertion that obstacle avoidance is a dorsal stream function. Schindler et al., tested two OA patients (AT and IG) and found that these patients "took no account whatsoever" (p. 780) of the varying positions of the obstacles during reaching, but were unimpaired when asked to bisect the space between the obstacles (Schinder et al., 2004). Figure 6.3, below, presents the mean responses in both the reaching

(plot a) and bisection (plot b) tasks for the two OA patients, with control performance plotted for reference.

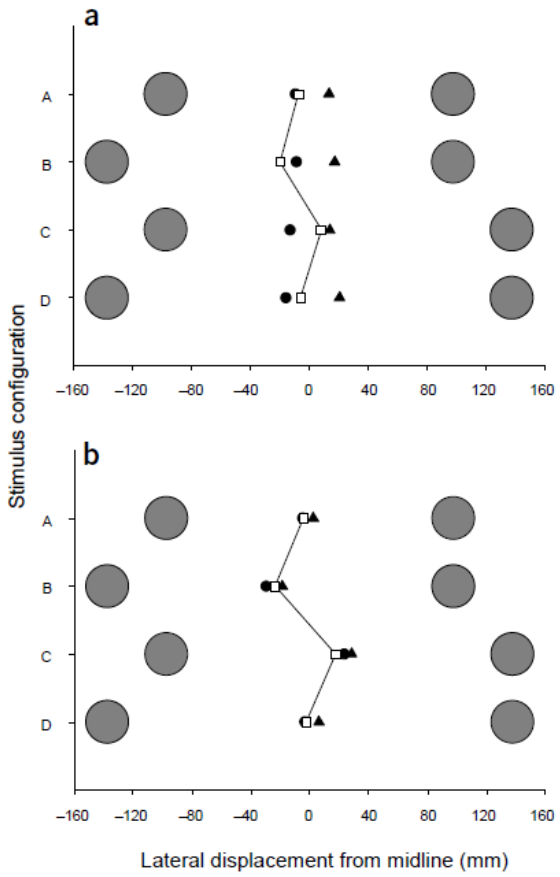


Figure 6.3: Mean Responses in (a) Reaching and (b) Bisection Tasks for Patients IG and AT with Control Performance (from Schindler et al., 2004).
Note: Control performance is based on the mean scores from 8 controls. Dark grey circles represent the stimulus cylinder (obstacle) locations in the four configurations.
Key: ● = patient IG, ▲= patient AT, □ = mean control performance.

Performance from both OA patients can be seen to remain relatively static in the reaching condition, remaining around the midpoint of the board, whereas control reaches account for the changing positions of the obstacles, adjusting to be around the midpoint between the obstacles (Schindler et al., 2004). In contrast, there was no difference between the OA patients and controls on the bisection task (Schindler et al., 2004).

These results have been replicated in subsequent studies of obstacle avoidance in OA patients (Rice et al., 2008; Cavina-Pratesi, Connolly & Milner, 2013). Similarly to pointing and grasping tasks, an improvement in performance has been observed for OA patients following a delay between stimulus presentation and the reaching movement for obstacle avoidance (Rice et al., 2008). Performance on obstacle avoidance has not, at the time of writing, been tested for patients with PCA. PCA patients who exhibit symptoms of OA would be expected to fail to account for the changing positions of the obstacles, with no significant variation in reach trajectories between different obstacle configurations.

6.0.3 Aims

The primary aim of the experiments reported within this chapter was to investigate the visuomotor deficits associated with PCA in a manner more detailed than prior investigations of these abilities in PCA. The visuomotor deficits of interest are primarily those associated with profiles of OA, namely; misreaching to targets in the visual periphery, impaired grip scaling in object grasping, and deficits in the automatic avoidance of obstacles. The secondary aim is to determine whether OA-like symptoms are present in patients with diagnoses other than PCA.

6.1 Method

6.1.1 Ethical Approval

See Chapter 4, Section 4.1.1 for details.

6.1.2 Recruitment

Clinical recruitment was conducted according to the outline provided in Chapter 5, Section 5.1.2.

6.1.3 Participants

See Chapter 5, Section 5.1.3 for details on clinical and control participants, and an overview of patient characteristics within the Phase 2 testing sample.

6.1.4 Analysis Methodology & Justification

Control data were used in order to characterise 'normal' performance for each task. These results were then used in order to generate cut-offs for normal performance (see Chapter 4, Section 4.2.1 for a detailed description of cut-off score generation).

6.2 Grasping & Perceptual Matching Task

6.2.1 Procedure, Materials & Measures

This task was a simple grasping and perceptual matching task, where participants were required to reach out in front of them and grasp Efron blocks of different sizes (grasping task), or indicate by adjusting the aperture between their thumb and index finger their estimate of the size of the block presented (matching task).

In order to determine which Efron blocks should be used in the experimental set, an initial pilot study was performed with 10 healthy volunteer participants. These participants were presented with each of the seven sizes of Efron blocks (A-G) in pseudorandom order. Starting with a pinched grip, participants were

asked to reach out and grip each block with their right hand 'as if [they] were going to pick it up'. Motion recordings were taken of the thumb and index finger of the grasping hand, and used to determine which block sizes would provide the best overview of patient performance. Correlation coefficients of MGA to block size were used to determine the best stimulus set to use experimentally. The strongest correlations were obtained by using a reduced stimulus set containing the 'whole size' blocks only. This also enabled fewer stimuli to be used, which in turn ensured that the test would be as brief as possible, thus benefiting patients. Therefore, block sizes A, C, E and G were selected.

As detailed above, a set of four Efron blocks was used for the grasping and matching tasks. Efron blocks are matched for surface area, texture, mass and colour and vary only in width and length. The blocks used, and their associated dimensions, are presented in Table 6.1, below.

Efron Block	Width	Length	Approximate Scaled Representation
A	50mm	50mm	
C	40mm	62mm	
E	30mm	85mm	
G	20mm	125mm	

Table 6.1: Efron Block Characteristics

In both the grasping and matching task participants were seated at a table with a starting marker 50mm in front of them. Recordings were taken using an Optotrak Certus Motion tracker, and were taken from both hands, using one strober. The strober had six connected markers, three of which created the rigid body of the table that the screen was presented on. The last three markers were connected to the participant's wrist, index finger and thumb on the hand to be recorded. The collection frame frequency was 200Hz for markers, set at 39% power.

Blocks were presented in central, not peripheral, vision. The initial design of the experiment called for blocks to be presented in central as well as left- and right-lateralised peripheral vision. However, it was not possible to do so in practice, as patients found comprehending the changing instructions between each condition too challenging.

In the grasping task participants started each trial with their index finger and thumb gently pressed together on the starting marker. The experimenter placed the block in front of the participant, at a distance of 20cm, and pressed a button to initiate the recording sequence. Once the button was pressed an auditory 'beep' sounded, which was the cue for participants to initiate the grasping movement. A further 'beep' sounded after 3000ms which indicated the end of the trial, at which point the participant would return their hand to the starting posture. The experimenter would then remove the Efron block and start the next trial. Usually, a task such as this one would require participants to start each trial with their eyes initially closed, however this proved too complex for patients (who repeatedly failed to open their eyes in time for the start of the trial), therefore this requirement was removed.

The matching task followed the same task procedure with slightly amended instructions. Participants were asked to keep their hand over the starting marker and indicate, by adjusting the aperture of their thumb and index finger, their estimate of the size of the presented block.

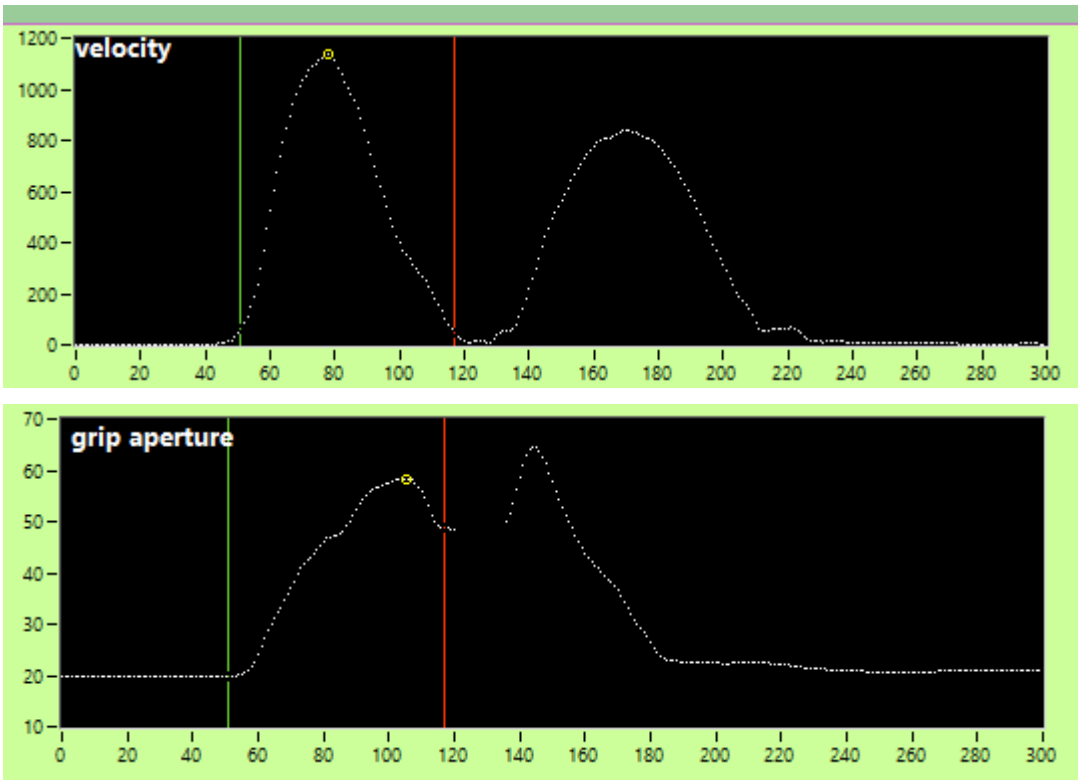
The grasping and matching tasks each included two experimental blocks - one for each hand. The Efron blocks were presented in pseudorandom order and each appeared five times per block. The original experimental design called for the blocks to be presented in the following order; grasping right hand, matching right hand, matching left hand, and then grasping left hand. However, in practice the task switching was too challenging for patients, therefore the blocks were presented as; grasping right hand, grasping left hand, matching right hand, and matching left hand.

6.2.2 Analysis

Data were first analysed using a specialised kinematic analysis computer program. Each grasping and matching movement was individually visually inspected in turn to ensure that the trial began with a pinched grip, and to verify that the maximum grip aperture (MGA) (grasping) or maximum aperture (MAP) (matching) were accurately captured by the individual recording file. The velocity profile of each trial was also visually analysed in order to ensure that the trial data ended with the terminus of the grasping movement, and that any return transit of the hand back to the start position was not captured in the resulting output file. Following kinematic analysis of each trial for each participant, the resultant output files were used in further analysis.

For grasping trials, the movement was defined as the portion of the movement starting when the velocity exceeded 50mm/s, and ending when the velocity was less than 50mm/s. Matching trials involved identifying the stable portion of the movement recording which was the participant indicating their estimate of the size of the block. Figure 6.4, below, presents example profiles of grasping and matching kinematic analysis plots.

A)



B)

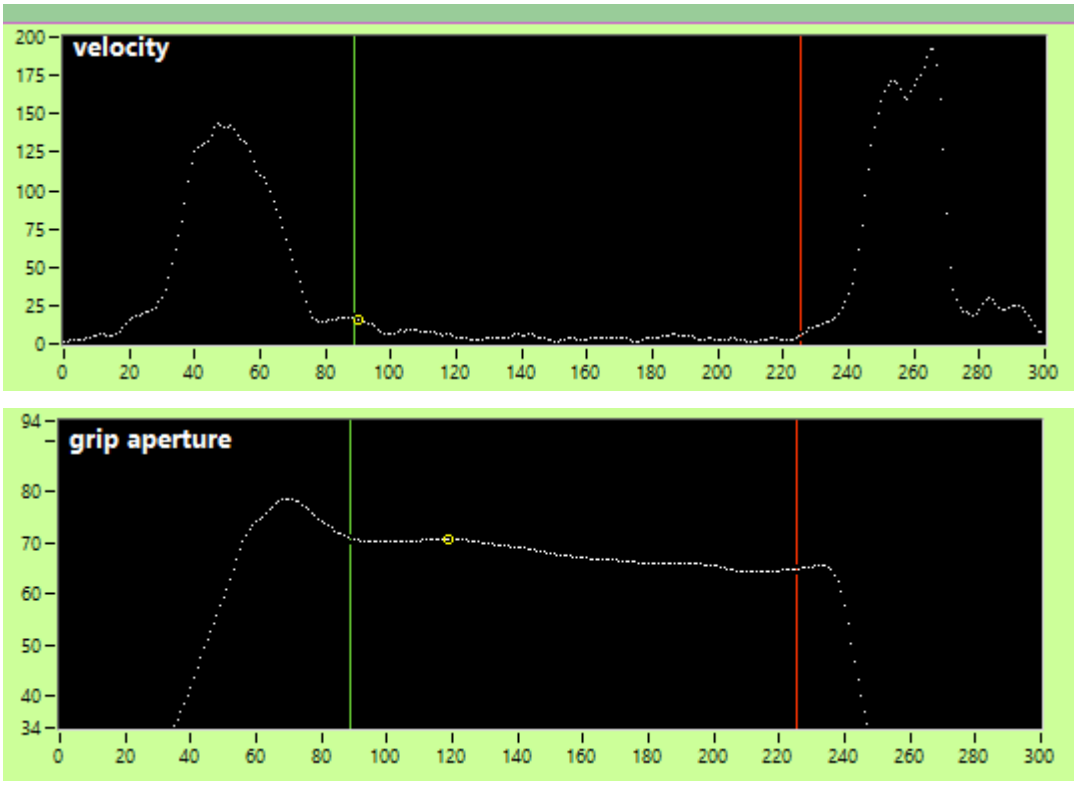


Figure 6.4: A) Grasping and B) Matching Kinematic Analysis Movement Profile Plots
Note: Green vertical line indicates start point of analysed trial, red vertical line indicates end point of analysed trial, yellow circle indicates peak value (for velocity/grip aperture).

The dependent variables of interest within this study were the MGA for grasping trials, and MAP for matching trials. MAP was calculated as the mean grip aperture between the manually-adjusted start and end point of each matching trial.

An initial data cleaning exercise was conducted, in which the following exclusion rules were applied:

Dependent Variable	Exclusion Rule	Justification	No. of cases excluded (% of total trials)
Stimulus Code	If the stimulus presented was not recorded, exclude these trials from further analysis.	Without information on what size of stimulus participants were grasping (due to experimental error) the trial data is rendered meaningless.	13 (0.60%)
Maximum Aperture (MAP)	If no value is recorded for MAP, exclude the trial.	If no data are recorded on MAP (due to a marker being occluded during recording), analysis of grip scaling cannot be completed, therefore this trial is removed.	40 (1.85%)
Maximum Grip Aperture (MGA)	If MGA > 100, exclude the trial.	MGA > 100mm are likely to be invalid, thus are filtered out.	4 (0.18%)
N/A	If participants have not completed two conditions for at least one hand, exclude all data from this participant.	Participants who have not completed both conditions with at least one hand have incomplete data, making comparative analysis on performance between grasping and matching impossible, therefore these participants are excluded from further analysis.	23 (1.06%) (Participants 1 and 18)

Table 6.2: Grasping Task: Data Cleaning Exclusion Criteria

6.2.3 Results

Initial group level exploratory analyses were conducted in order to characterise control performance on the grasping task and matching tasks, using a multiple regression to predict maximum grip aperture (MGA, in the grasping condition) or maximum aperture (MAP, in the matching condition) based on stimulus size and hand. A conservative alpha criterion of 0.005 was applied to these analyses in order to minimize the risk of Type I errors due to multiple comparisons.

Control MGA was significantly predicted by stimulus size and hand, $F(2, 671) = 178.874$, $p = 0.000$, $R^2 = 0.348$, with only stimulus size contributing significantly to the model ($p = 0.000$ for stimulus size, $p = 0.022$ for hand). Control MAP was also significantly predicted by both stimulus size and hand, $F(2, 701) = 634.883$, $p = 0.000$, $R^2 = 0.644$. Similarly to the grasping task, only stimulus size contributed significantly to the model ($p = 0.000$ for stimulus size, $p = 0.024$ for hand).

Individual regression analyses were conducted for each participant (patient and control) predicting MGA/MAP by both stimulus size and hand in order to determine whether patients demonstrated grip scaling under both grasping and matching conditions, and in order to produce slope coefficients to enable a slope comparison analysis to be conducted (see Chapter 5, Section 5.3.3.2 for further details on the methods of this analysis) (Crawford & Garthwaite, 2004).

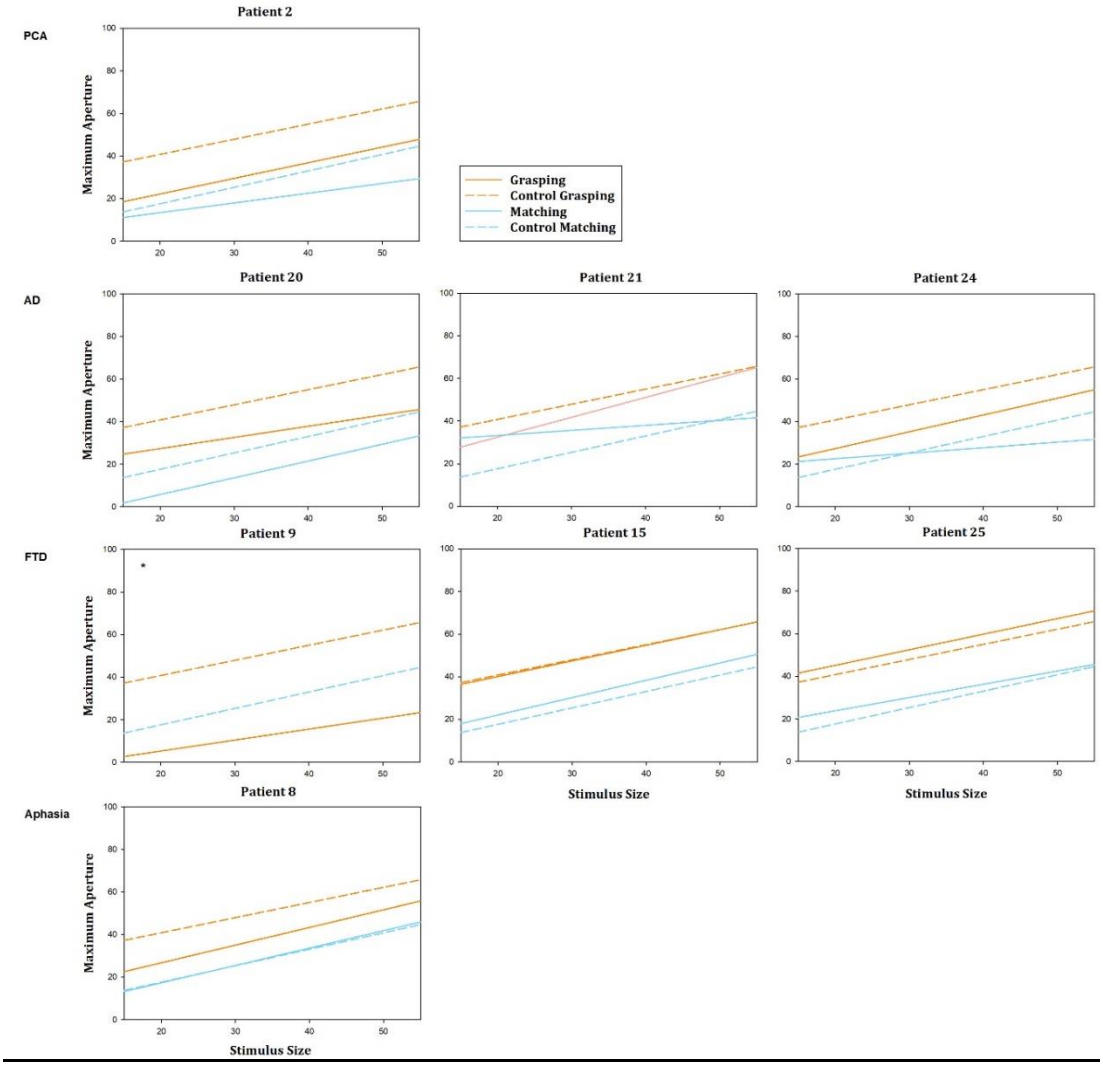


Figure 6.5: Linear Regression Lines for Grasping and Matching
* Patient 9 did not complete the matching condition.
Note: 'Maximum Aperture' is MGA for grasping task, MAP for matching task.

Figure 6.5, above, presents individual regression data for each patient. All patients demonstrated significant grip scaling in the grasping condition, and all but two patients (21 and 24, both AD) demonstrated significant scaling in the matching condition. This may be indicative of a perceptual deficit for these two patients.

The regression lines plotted in Figure 6.5 suggest that patients have generally smaller maximum apertures when compared to controls. Non-parametric Mann-Whitney *U* Tests were conducted on MGA and MAP scores between

patients and controls, using an alpha criterion of 0.05. A statistically significant difference between patients (median = 37.58) and controls (median = 51.67) was observed for MGA in the grasping condition, $U = 70299.00$, $p = 0.000$. Similarly, a statistically significant difference was also observed between patients and controls (median = 26.29 and 28.61, respectively) for MAP in the matching condition, $U = 96746.50$, $p = 0.000$. Therefore, patients had significantly smaller maximum apertures under both conditions when compared with controls.

Bartlett's test for sphericity was not significant for either MGA, X^2 (17) = 7.80, p = 0.971, or MAP, X^2 (17) = 4.41, p = 0.999: therefore it was possible to conduct a slope comparison analysis between controls and individual patients. Results of these analyses are presented in Figure 6.6, below.

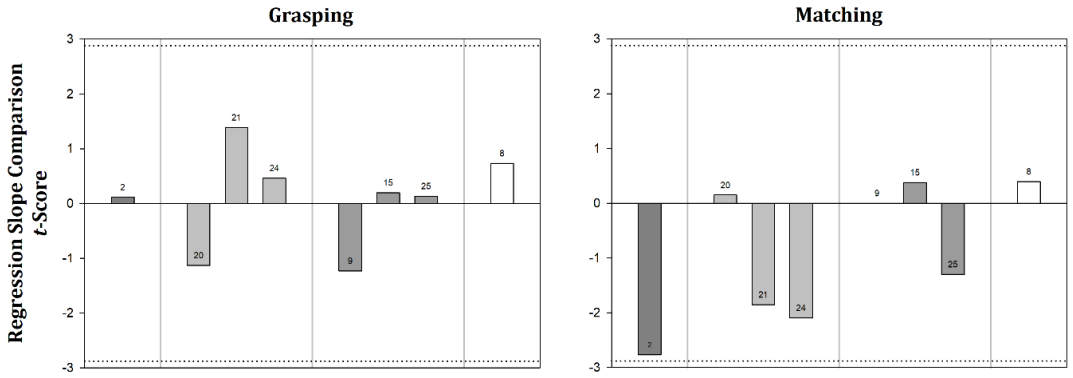


Figure 6.6: Slope Comparison Analysis *t*-Scores for Grasping and Matching
Key: · · · · · represents upper and lower critical value of *t.*
Subscripted labels refer to patient number.
Note: Patient 9 did not complete the matching task.

Patient slopes did not differ significantly from controls in the grasping task. In the matching task, only patient 2 (PCA) had a regression slope which differed significantly from controls (p = 0.000). Patients 21 and 24 also demonstrated more extreme *t*-scores than other patients on the matching task, however the regression slopes for these individuals did not differ significantly from controls

(p = 0.080 and p = 0.064, respectively). These results suggest that these patients may be exhibiting perceptual deficits, whereby their estimate of the size of the block is abnormally small and does not correlate as strongly to the true stimulus size, when compared to control estimates. Indeed, inspection of the regression slopes in Figure 6.5, above, for these patients indicates very little relation between stimulus size and maximum aperture in the matching task.

Overall, these results indicate that all patients demonstrated grip scaling within normal control limits in the grasping task. Similarly, most patients demonstrated significant scaling in the matching task with the exception of the one PCA patient who completed the task, as well as two AD patients, in whom there was no evidence of scaling (patients 1, 21 and 24).

6.3 Obstacle Avoidance Task

6.3.1 Procedure, Materials & Measures

The obstacle avoidance task was a simple reaching task in which participants were required to move their hand through a gap between two obstacles to touch a distal target area.

The obstacle avoidance task required participants to be seated at a table with an obstacle avoidance board (600 x 600mm) immediately in front of them, aligned with the front edge of the table (see Figure 6.7 for a representation of the board). Participants were required to place the index finger of their dominant hand on the starting position (represented by an 'X' on Figure 6.7). The experimenter would then count down, saying "three, two, one, go". When the experimenter said "go" the participant reached forward and touched the back of the board with their index finger. The experimenter would press a button to trigger the motion recording one second before the "go" command, in order to ensure that the movement was captured. Each recording lasted 3000ms. After

each trial, the experimenter would remove the obstacles and reposition them for the next trial.

The independent variables in this task were the position of contralateral obstacle and the position of the ipsilateral obstacle. The possible combination of obstacle positions are presented below, from a participant's perspective:

- Left far, right near (positions A and C)
- Left far, right far (positions A and D)
- Left near, right near (positons B and C)
- Left near, right far (positions B and D)
- Dowels absent, no obstacles on the board

Dowel position conditions were presented in pseudorandom order. Each condition was presented 12 times, with a total of 60 experimental trials.

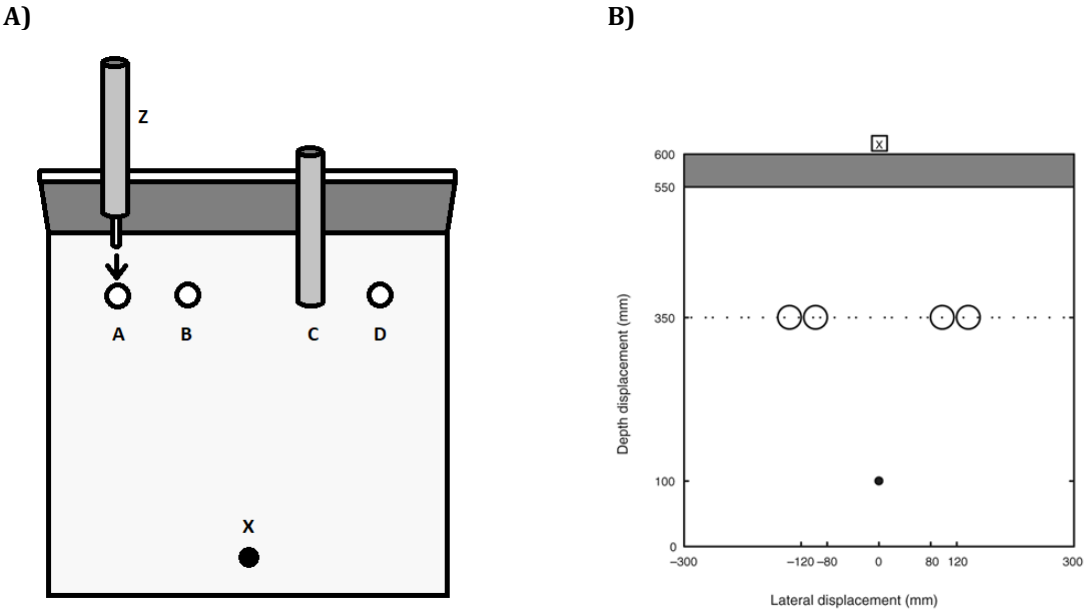


Figure 6.7: Obstacle Avoidance Task: (A) Picture Representation of Experimental Set-up and (B) Board Dimensions
(A) Z is a movable obstacle. A-D are the possible locations of the dowels, X is the starting position.
(B) Board dimensions image taken from Schindler et al., 2004. Open circles represent possible locations of the two dowels. The black dot is the starting position, and the cross is the point of fixation at the back of the board.

Recordings were taken using an Optotrak Certus Motion tracker. Data were recorded using one strober. The strober had four connected markers, three of which created the rigid body of the table that the obstacle avoidance board was presented on. The last marker was connected to the participant's index fingers on their dominant hand in order to record their reaching movement. The collection frame frequency was 200Hz for markers, set at 39% power.

6.3.2 Analysis

Initial kinematic data analyses were conducted in order to parse the forward movement of the finger from the total movement recorded during each trial. Patient 4 was removed from further analysis following this stage of data preparation, as the patient failed to make forward movements on the majority of trials – instead demonstrating meandering, uncertain movements across the board, rarely terminating the movement in the distal target area. Therefore, this participant was unable to meaningfully interact with the task.

Following this, data were spatially normalised in order to allow for the extraction of the dependent variable of interest, namely, the co-ordinates of the finger when crossing the mid-point between the obstacles (the transection point).

Following spatial normalisation, data were cleaned prior to analysis according to the rules outlined in Table 6.3, below.

Dependent Variable	Exclusion Rule	Justification	No. of cases excluded (% of total trials)
Misalignment	Optotrak recording numbers which do not align with trial ID numbers are excluded from the positive checkpoint onwards for that participant.	During recording, regular recording checks were made to ensure that Optotrak recording numbers aligned with trial ID numbers. When recording errors occurred (as a result of experimental error), misalignments resulted, therefore trials are excluded after the point at which the trial ID and Optotrak recoding numbers last aligned.	292 (15.45%)
Miss-trial	Trials recorded as miss-trials during kinematic movement analysis are excluded from further analysis.	Trials are removed for which no movement data are available as a result of the missing data in the movement, or the movement being missed entirely.	2 (0.11%)
Transection point data	If no data are available for the co-ordinate of the transection point of the movement, exclude trial from further analysis.	If data are not available for the transection point then interpretation of the influence of the obstacle positions on this point is not possible.	30 (1.59%)

Table 6.3: Obstacle Avoidance Task: Data Cleaning Exclusion Criteria

Movement transection points were subsequently transformed in order to be relative to the zero co-ordinate, which was the middle of the stimulus board. Stimulus positions were coded according to side, with ipsilateral obstacles coded as positive, and contralateral obstacles coded as negative.

Individual linear regressions were run in order to determine the effect of ipsilateral and contralateral stimulus positions on response transection points. The slope coefficients for both the ipsilateral (IOP) and contralateral obstacle position (COP) variables represent the relative weightings of each on the response endpoints, ipsilateral obstacle weighting (IOW) and contralateral

obstacle weighting (COW). These IOW and COW values were then used to calculate avoidance sum (AvS) and avoidance bias (AvB).

The AvS provides a measure of how much obstacle avoidance was observed, with lower values indicating less avoidance manoeuvres. The formula for the calculation of AvS is presented below.

$$AvB = (IOW + COW)$$

The AvB value provides an indication of whether the ipsilateral or contralateral obstacles had a greater influence on response transection point. Negative AvB values indicate a greater influence of contralateral obstacles, and positive AvB values indicate a greater influence of ipsilateral obstacles. The formula for the calculation of AvB is provided below.

$$AvB = (IOW - COW)$$

6.3.3 Results

Control performance was characterised initially, in order to gain an overview of normal performance on this task. Only stimulus-present trials were analysed, as these trials contained the movement data which were of interest - the avoidance of obstacles. A multiple linear regression was conducted, predicting transection point by IOP and COP. The results indicated a significant regression equation, $F(2, 779) = 49.504$, $p = 0.000$, with an R^2 of 0.113. The IOW was 0.303 and the COW was 0.264, both significant at $p = 0.000$. These results therefore found that control responses were significantly influenced by the IOP and COP (with significant main effects of both), indicating clear obstacle avoidance, and that controls were influenced more strongly by the ipsilateral obstacle position than the contralateral.

Figure 6.8, below, presents median control response endpoints for each combination of stimuli positions, and further illustrates the clear pattern of obstacle avoidance for controls, with a greater influence of IOP over COP on transection responses.

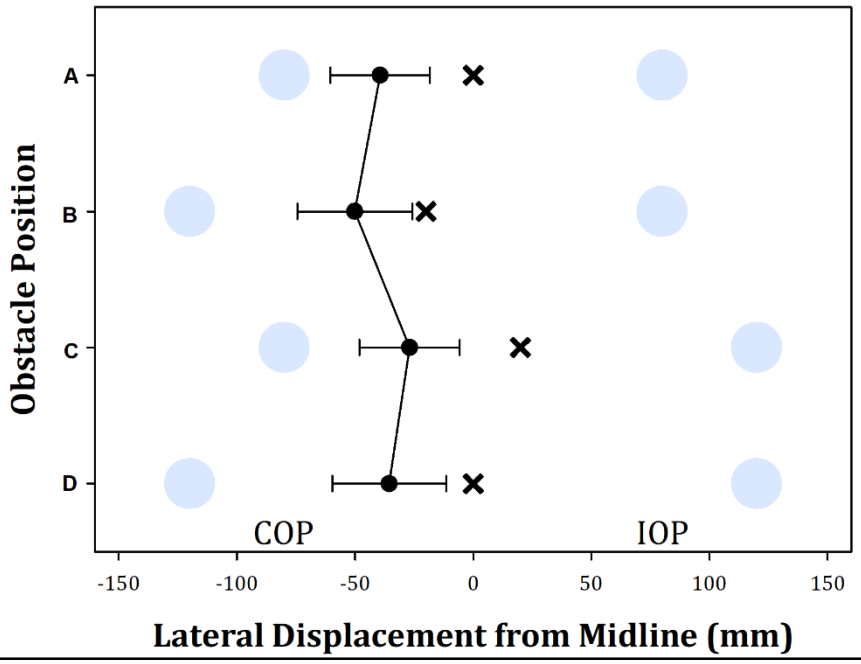


Figure 6.8: Control Median Transection Points (with standard deviation).
Key: COP = contralateral obstacle position, IOP = ipsilateral obstacle position.
Note: Blue circles represent position of stimuli for each obstacle position code (A-D).
Key: **X** = true midpoint between obstacles (for reference).

AvS is proposed as a measure of overall object avoidance, similar to the EWB and EWS measures of line bisection proposed by McIntosh et al. (McIntosh, Shindler, Birchall & Milner, 2005). If responses move in the same direction as obstacles on either the ipsilateral or contralateral side, the weighting will be more positive, therefore a higher AvS indicates more overall obstacle avoidance. An AvS of 0 indicates no obstacle avoidance. AvB is proposed as a measure of lateral asymmetry in avoidance behaviour, with more positive numbers indicating a greater influence of IOP, and more negative numbers indicating a greater influence of COP.

Individual linear regressions were performed for each patient and control. The results of these linear regression analyses were then summarized at the group level for controls.

The control mean AvS was 0.56 (SD = 0.220), indicating clear obstacle avoidance behaviour. Control mean AvB was 0.05 (SD = 0.183). A *t*-test was conducted which indicated that control AvB did not differ significantly from zero, $t(17) = 1.073$, $p = 0.298$. Therefore, controls did not demonstrate a significant influence of either the IOP or COP on behaviour.

In order to gain an initial overview of performance by patients, median transection positions were plotted against cut-offs for normality generated from control performance (see Figure 6.9, below).

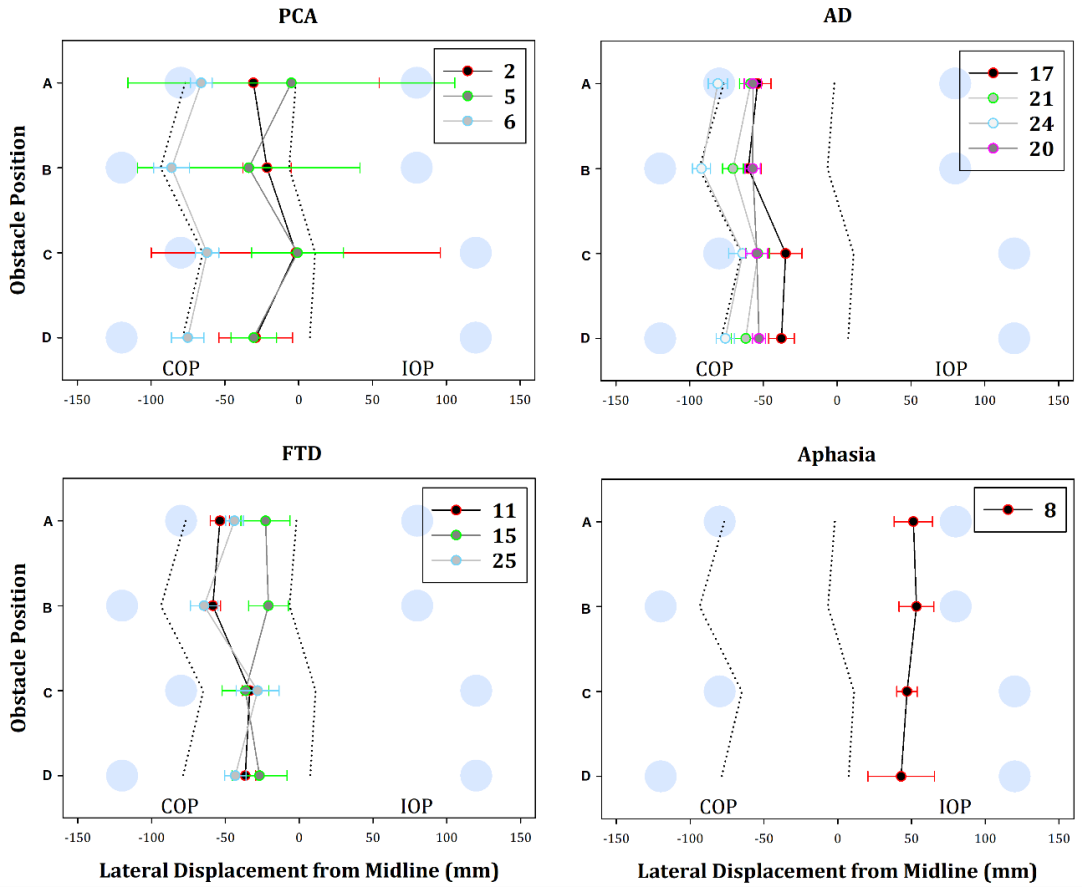


Figure 6.9: Patient Median Transection Points (with standard deviation).
Key: COP = contralateral object position, IOP = ipsilateral object position, · · · · · represents boundaries of normal performance.
Note: Blue circles represent position of stimuli for each obstacle position code (A-D).

These results indicate some interesting initial findings. All three PCA patients who completed this task responded within normal limits, although patient 6 appeared to respond to the extreme contralateral side of space. Results from PCA patient 2 may indicate impaired obstacle avoidance. Patient 5 appears to demonstrate intact obstacle avoidance, although the response variability was high.

AD patients also responded within normal limits, although all four appeared to respond more towards the contralateral side of space. All AD patients appear to demonstrate intact obstacle avoidance, with the exception of patient 20, in whom there appears to be evidence of impairment. FTD patients also performed within normal limits, although patient 25 appears to show impaired obstacle

avoidance. Aphasic patient 8 responded well out-with normal limits, also appearing to demonstrate impaired obstacle avoidance.

In order to formally assess whether patients demonstrated obstacle avoidance, AvS and AvB are plotted in Figure 6.10, below.

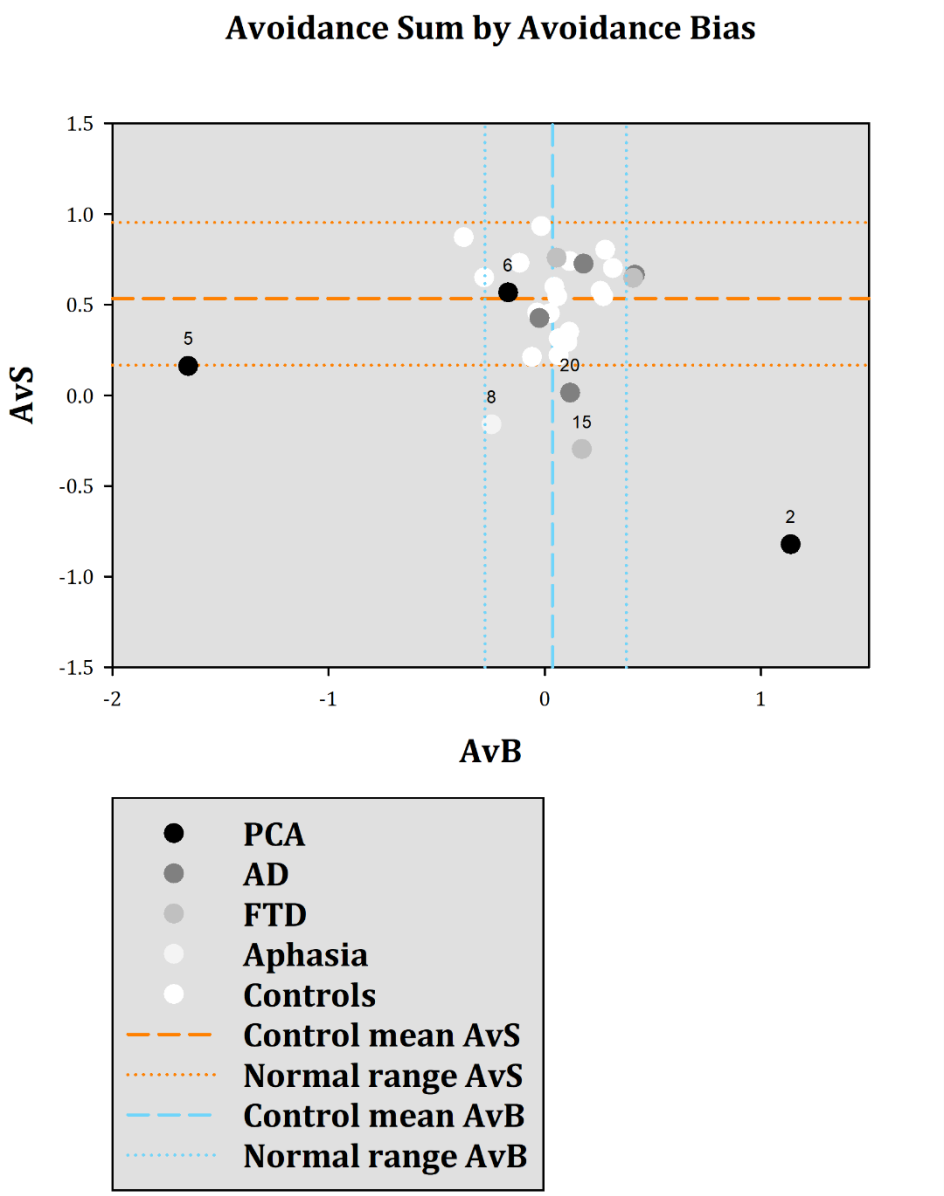


Figure 6.10: Obstacle Avoidance Sum (AvS) by Obstacle Avoidance Bias (AvB). Superscripted labels refer to patient number for all PCA patients (2, 5, 6) and anomalous performers.

Individual linear regression analyses were calculated on transection point predicted by IOP and COP. These regression equations were significant in every

case, with the exception of PCA patients 2 and 5, AD patient 20, FTD patient 15, and aphasic patient 8. These patients therefore demonstrated abnormalities of implicit avoidance of obstacles, which are problematic to meaningfully interpret as interpretation of the characteristics of their avoidance behaviour is contingent on the linear regression equation reaching significance. Interpretation of the patterns of behaviour observed are presented below, with the caveat that these results must be interpreted with caution, given the non-significant regression equations for these individuals.

Of the PCA patients, two out of three patients showed abnormalities indicating a lack of implicit avoidance of obstacles (patients 2 and 5), falling well below the normal range on AvS. Both of these patients also demonstrated abnormalities in AvB, indicating abnormally high weightings to the COP for patient 5, and abnormally high weightings to the IOP for patient 2. PCA patient 6 appeared unimpaired, performing at the level of controls on this task – indicating intact obstacle avoidance.

Of the AD patients, only one patient demonstrated abnormalities which may indicate a lack of obstacle avoidance (patient 20). This patient demonstrated an AvS below the lower cut-off for normality, but AvB within the normal range. FTD patient 15 and aphasic patient 8 also demonstrated AvS below the lower cut-off for normality, but normal AvB. These patients may also be considered to have abnormal obstacle avoidance, showing an absence of avoidance behaviour.

6.4 Pointing Task

6.4.1 Procedure, Materials & Measures

This task was a simple pointing task in which participants were required to reach out and touch white target circles which appeared on a touchscreen under two different experimental conditions; 'look and point', and 'no look and point'.

The experiment comprised two epochs (right and left hand), with four experimental blocks (2 blocks per condition, presented in ABBA order) and an additional practice block presented at the start. Table 6.4, below, presents the task parameters and instructions of each block.

Block	Parameters	Instructions
Practice	No fixation cross (NF)	Look at the target when it appears, and point (touch).
A	Flashing white fixation cross (free vision)	Look at the target when it appears, and point (touch).
B	Flashing white fixation cross (central fixation)	Fixate on cross, and point (touch).

Table 6.4: Pointing Task Block Parameters and Instructions

Each target appeared four times (plus an additional 1 time during the practice block) for each hand. Therefore, each block presented each target location once. This limited set was used in order to reduce the time taken to complete this task, and therefore minimize burden and fatigue for patients.

The task involved participants reaching out with their index finger from a marked starting position (~50mm in front of the body, 570mm in front of the screen) to touch a white circle stimulus which would appear on screen – with a concurrent electronic 'beep' sound – as quickly and as accurately as possible. Once the participant touched the screen the experimenter would manually accept or 'recycle' the trial. Trials which were recycled were cycled back in to the stimulus set and presented again. The experimenter would then press a button to advance to the next trial sequence. Once the next trial sequence was initiated and the fixation cross presented, there would be a pre-programmed delay of 2000ms after which the auditory 'beep' would sound as the target appeared. A TTL pulse was sent to the motion tracker in tandem with the beep and appearance of the target – which triggered the motion tracker to record for 3000ms in order to capture the trial movement. Target locations were fixed, but presented in a random order within each block. The pointing task was programmed using PsychoPy.

Trials were recycled if participants did not comply with the fixation rules for the task. This was monitored on-line using a pair of SMI Eye Tracking Glasses connected to a laptop which the experimenter observed during each trial. The SMI glasses were also used to record the eye movements of participants during the experiment. These recordings were reviewed after the experiment and used for quality assessment of the data, and to exclude rogue non-conforming trials. The recordings were assessed using the SMI software package 'BeGaze'.

Stimuli were presented at 16 different target locations across four radial arms (see Figure 6.11 in Section 6.4.2, below).

The 'touch' stimuli were white circles, 20mm in diameter (approximately the size of the end of a finger) and disappeared immediately when a touch was detected on screen. Following each trial a grey screen was presented in order to prevent dark-adaptation between trials. The white central fixation cross was 50mm in diameter (when present), and 'flashed' on for 500ms, followed by a pause of 500ms, repeatedly.

Data were recorded using two strobers. The first strober had four connected markers, which formed the rigid body of the touchscreen (rigid bodies were created using NDI 6D Architect). The second strober had five connected markers, three of which created the rigid body of the table on which the screen was presented. The last two markers were connected to the participant's index fingers on each hand. The collection frame frequency was 200Hz for markers, set at 39% power. Recordings were taken using an Optotrak Certus Motion tracker.

6.4.2 Analysis

Initial data cleaning exclusion rules were applied prior to analysis, using the criteria outlined below.

Dependent Variable	Exclusion Rule	Justification	No. of cases excluded (% of total trials)
N/A	If participants have not completed at least two conditions for at least one hand, exclude all data from this participant.	Participants who have not completed at least two out of three conditions with at least one hand have incomplete data making comparative analysis on performance between conditions impossible, therefore these participants are excluded from further analysis.	147 (2.74%) (Participants 4 and 18)
Transformed Y Co-ordinate	If the Optotrak transformed Y co-ordinate of the point is <-20, exclude this trial from analysis (where touchscreen endpoints cannot be used)	In cases where the Optotrak is used to determine the endpoint of reaches (due to touchscreen malfunction), reaches that have a transformed Y co-ordinate of <-20 are excluded, as this movement ends 2cm or further from the screen surface, therefore this is not a reliable measure of the actual response endpoint.	285 (5.30%)
Target Location	If no touchscreen output are available for a trial, exclude this trial from further analysis.	If no data are available on target location (due to an output error from the touchscreen), then analysis of the endpoints relative to the target are not possible.	552 (10.27%)
Kinematic False Trial	If the trial is labelled 'false', exclude this trial from further analysis.	Kinematic data labelled 'false' were determined as misrecordings, or recordings with no useable data during the kinematic analysis, and are thus excluded from further analysis, unless touchscreen data are available for this trial.	113 (2.10%)

Table 6.5: Pointing Task: Data Cleaning Exclusion Criteria

Due to an unavoidable monitor change during the course of testing, the controls were run on a different touchscreen which could not deliver the same resolution, meaning the controls were presented with an expanded display relative to patients. However, this analysis will still generate norms with respect to control performance as the expanded display will lead to more conservative estimates of abnormalities. Figure 6.11, below, presents the degrees of retinal eccentricity at which patient and control targets were presented, with associated target numbers. The targets were presented at four corresponding locations in each quadrant, approximately 1.5, 4.5, 7.7, and 10.8° retinal eccentricity for patients (15mm, 45.9mm, 77.1mm, and 108.9mm from fixation).

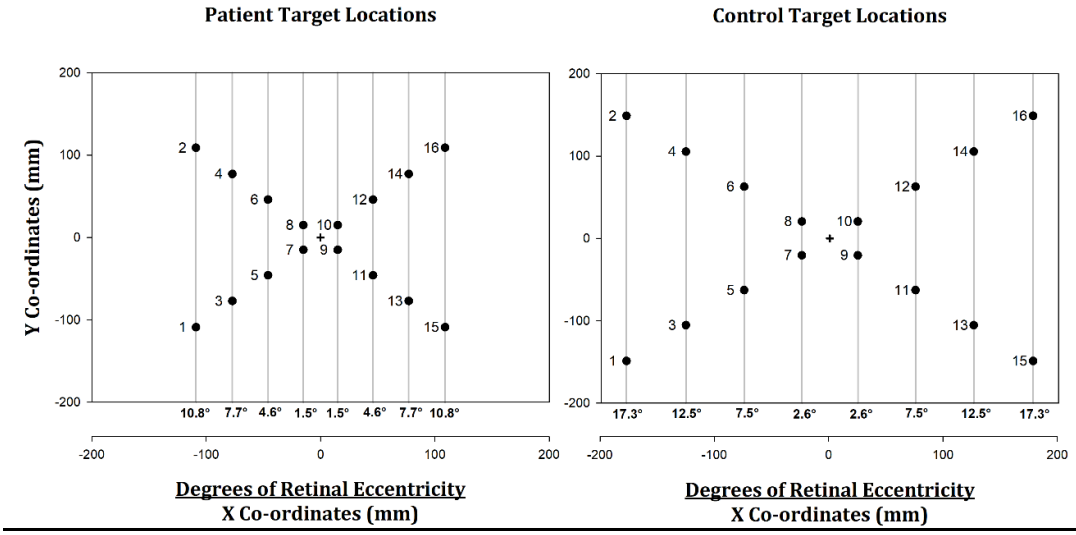


Figure 6.11: Target Location Co-ordinates with Associated Degrees of Retinal Eccentricity for Patients and Controls.
Note: Fix = fixation. Superscripted numbers refer to target location number.

In order to allow for comparison between controls and patients across target eccentricities, eccentricities were recoded from 1-4, as detailed in Table 6.6, below.

Eccentricity Code	True Target Eccentricity		Targets at Code Location
	Patient	Control	
1	1.5°	2.6°	7, 8, 9, 10
2	4.5°	7.5°	5, 6, 11, 12
3	7.7°	12.5°	3, 4, 13, 14
4	10.8°	17.3°	1, 2, 15, 16

Table 6.6: Eccentricity Codes for Target Locations

Endpoint data were used from the touchscreen where possible (6 patients, 17 controls; 50% and 94.5%, respectively). In cases where touchscreen data were deemed unreliable due to touchscreen malfunctions, pointing endpoints were extracted from the kinematic Optotrak recordings by transforming movement co-ordinates into the touchscreen frame of reference (6 patients, 1 control; 50% and 5.5%, respectively).

Absolute error was calculated using the following formula:

$$Absolute\ error = \sqrt{(response\ x + target\ y)^2 + (response\ y - target\ y)^2}$$

6.4.3 Results

The NF condition was a practice condition and was used in order to check the alignment of targets to responses, and thus to check the reliability of response data taken from the touchscreen. This condition was therefore omitted from further analysis. The two experimental conditions (free vision and central fixation) were used in subsequent analyses in order to assess the difference in error magnitude and characteristics between free and central vision (with greater errors predicted under central vision for OA-like presentations).

In order to provide a point of reference, control behaviour was initially characterised. Figure 6.12, below, presents mean endpoint co-ordinates for controls across each condition and hand.

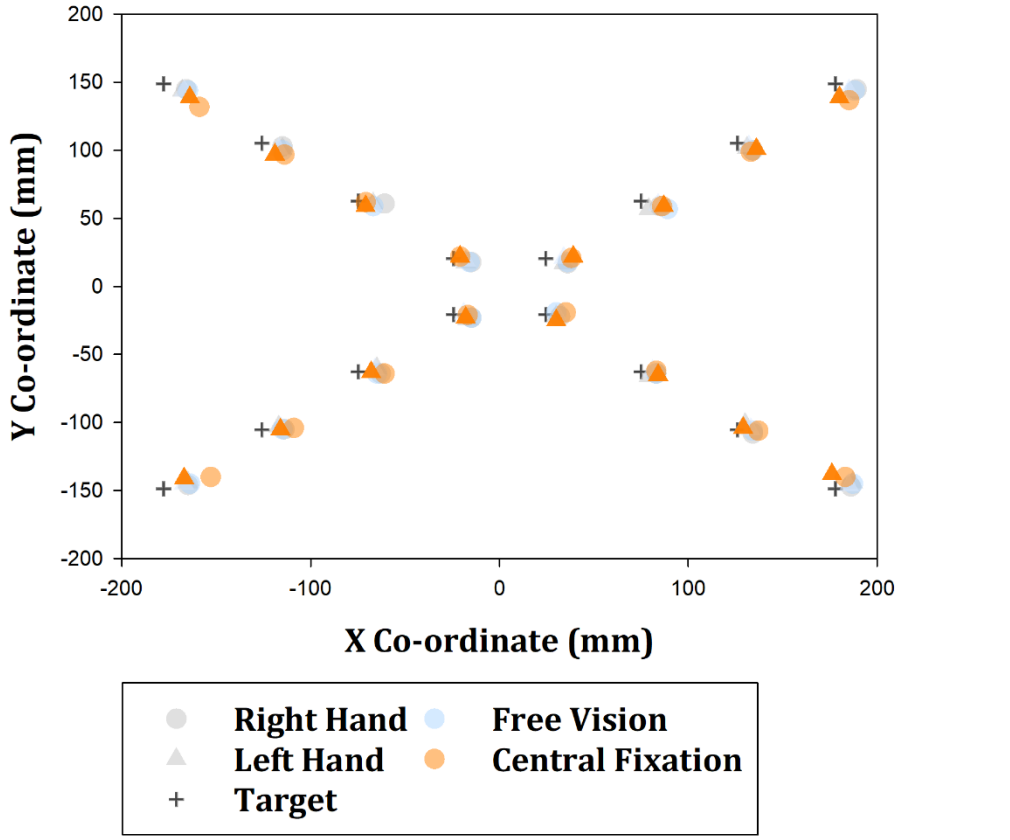


Figure 6.12: Control Mean Response Endpoints Across Pointing Conditions
Key: ● = right hand, ▲= left hand, blue = free vision, orange = central fixation.

Figure 6.12 appears to indicate no difference in response endpoints across target locations for controls. This figure does, however, indicate that responses are subject to consistent but small biases, most likely the result of the discrepancy between the true centre of the responding finger and the actual point of first pressure from the responding finger on the screen, thus leading responses to appear to be slightly misaligned from the true target locations.

Absolute error values were calculated in order to further assess for any differences in error magnitude between conditions, and are plotted for controls below in Figure 6.13.

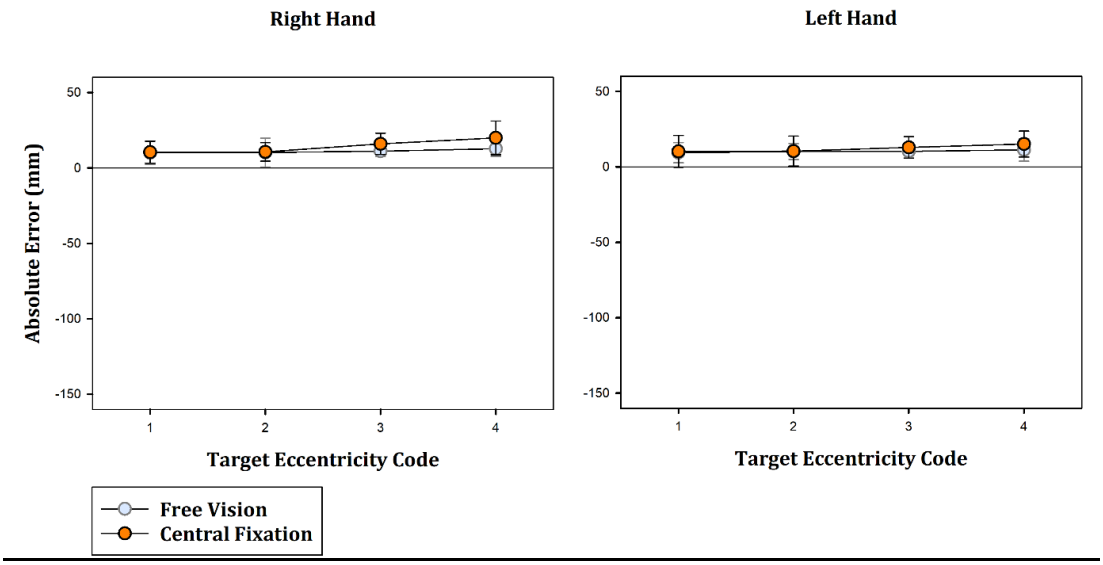


Figure 6.13: Control Amplitude Error Across Conditions (with Standard Deviation).

In order to assess whether absolute error was significantly different between conditions, target eccentricities, and responding hand, a repeated measures ANOVA was conducted. The results indicated a significant main effect of target condition, $F(1, 21) = 10.890$, $p = 0.003$, and a significant main effect of target eccentricity, $F(3, 19) = 5.835$, $p = 0.005$, but no significant main effect of hand, $F(1, 21) = 3.779$, $p = 0.065$. The interaction terms did not reach significance. These results indicate significantly greater absolute errors in the central fixation condition compared with the free vision, and significantly greater absolute errors at increasing target eccentricities.

In order to gain an overview into any possible optic-ataxic like hypometria from patients, plots were produced which illustrate the mean pointing endpoints for each hand across each condition (Figure 6.14, below).

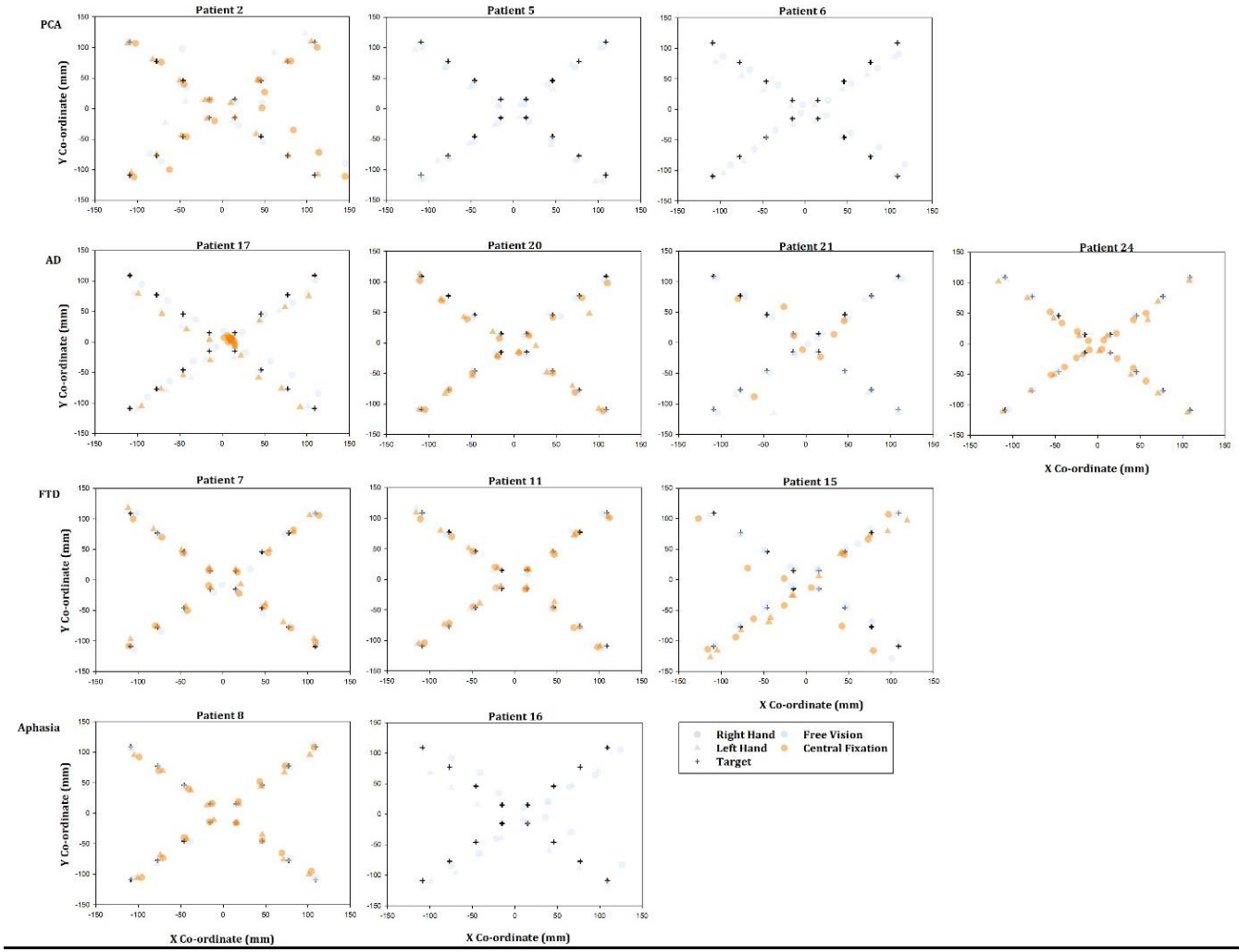


Figure 6.14: Mean Response Endpoints Across Pointing Conditions
Patients 5, 6 and 16 did not complete the NLP conditions. Patient 21 completed the NLP condition for the right hand only.

These plots present some striking initial results. Namely, that in three of the four AD patients there is evidence of strongly hypometric errors under central fixation (patients 17, 21 and 24), with dramatic magnetic misreaching for the right hand of patient 17, indicative of OA. One PCA patient completed both the free and central fixation conditions (patient 2). In this patient, responses appear disordered and generally inaccurate, with no immediate sense of OA-like pointing errors. In addition, there does not appear to be any evidence to suggest that FTD or aphasic patients in this sample demonstrate OA-like hypometric errors. Patient 16's responses are generally inaccurate, but do not appear to deviate towards fixation.

In order assess whether patients differed from controls between the free viewing and central fixation conditions, amplitude shift was calculated for patients between the conditions. Amplitude shift was calculated as the difference between the absolute error for the free vision and central fixation conditions at each target eccentricity.

Cut-offs for normality for each hand and target eccentricity were calculated using the method specified in Chapter 4, Section 4.2.1.

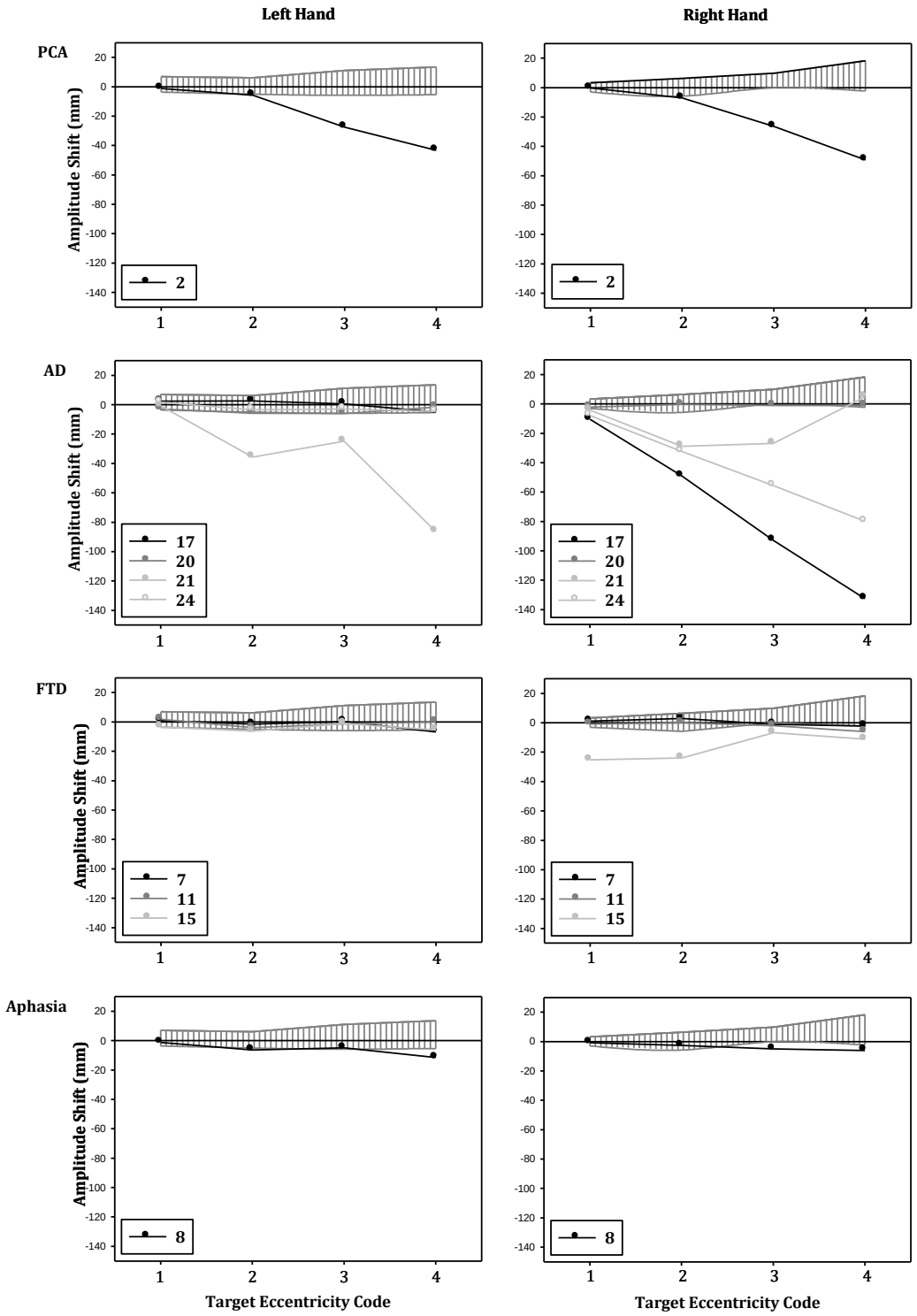


Figure 6.15: Amplitude Shift Between Free Vision and Central Fixation Conditions.
Note: Shaded area represents limits of normal performance.

Contradictory to initial impressions gained from Figure 6.14, PCA patient 2 appears to demonstrate OA-like hypometric pointing errors, with increasing

magnitude further from fixation. Patient 2 demonstrated OA-like pointing errors equally for both hands, possibly indicating no hand effect.

Perhaps more strikingly, Figure 6.15 serves to demonstrate the dramatically hypometric errors with increasing target eccentricity made by three of the four AD patients, which were well outside the cut-offs for normality, and indicative of OA. Two of these patients were impaired using their right hand only (patients 17 and 24), indicative of a hand effect, and one patient was impaired with both hands (patient 21). These results are not only very striking, but potentially important from a clinical perspective (see the discussion of this chapter for further elaboration).

FTD patient 15 fell below the cut-offs for normality using the right hand. However, these errors do not follow a typical pattern for OA, instead remaining relatively stable in terms of amplitude shift across all target eccentricities. Other FTD patients and aphasic patient 8 were unimpaired on this task, performing at the level of controls.

6.5 Discussion

The primary aim of the experiments reported within this chapter was to investigate the OA-like symptoms associated with profiles of PCA. In order to investigate these symptoms; grip scaling in object grasping, obstacle avoidance, and pointing to targets in the visual periphery were all investigated. The secondary aim was to determine whether OA-like symptoms were present in patients with diagnoses other than PCA.

6.5.1 Summary of Results

All patients demonstrated grip scaling in the grasping task which was equivalent to that of controls. Likewise, all patients demonstrated grip scaling in the perceptual matching task, equivalent to that of controls, with the exception

of two AD patients (patients 21 and 24), in whom no significant grip scaling was observed – and therefore in whom perceptual deficits may be inferred. The results also indicated that patients had significantly smaller maximum apertures when compared to controls. Only one patient demonstrated a regression slope which was significantly different from that of control participants (PCA patient 2), and this patient's regression slope differed from controls in the matching task only. The difference in slope between controls and patient 2 may be driven by the fact that this patient demonstrated a smaller maximum aperture of the hand overall and a much weaker correlation between maximum aperture and object size. This task was not an adequate test for OA, as it was not possible to present blocks in peripheral vision (where OA-like grip scaling deficits would be observed, if present), therefore this task should be considered more of a general investigation of grip scaling and perceptual matching. Thus, we cannot infer the presence of OA from results of this experiment.

On obstacle avoidance, two out of the three PCA patients who completed this task demonstrated impairments (patients 2 and 5). Both of these patients demonstrated abnormalities of AvS, indicating a lack of avoidance manoeuvres. These results therefore imply OA-like obstacle avoidance deficits in these patients. Abnormalities of AvB were also observed for these patients, with patient 2 demonstrating an extreme bias towards the IOP, and patient 5 demonstrating the opposite pattern, with a bias towards the COP. Interestingly, patient 2 was left-handed, and thus the IOP was also the left side. This patient has been noted to exhibit possible right-sided visual neglect in other assessments (see Chapter 5 and Chapter 7 for further details), which may account for the biased responding towards the left side of space.

One AD patient was abnormal (patient 20), with an AvS below the lower cut-off for normality. However, this patient demonstrated a normal AvB. These results imply a lack of avoidance behaviour for this patient, but no abnormal biases to either contralateral or ipsilateral obstacles. Similarly, one FTD (patient 15) and

one aphasic patient (patient 8) also showed the same pattern of impairment. Therefore only PCA patients demonstrated abnormalities of both total avoidance as well as laterally biased responding.

The potential of the AvS as a dependent measure on obstacle avoidance tasks is a noteworthy result from this study. Providing a reflection of total avoidance behaviour, the AvS is a conceptually neat dependent measure. OA-like deficits in obstacle avoidance are not reported to be characterised by a bias to either side of space, thus the AvS is a clearer measure of whether a participant is accounting for the moving positions of the obstacles when compared to AvB (although AvB does provide insight into lateral asymmetry). Interestingly, on the pointing task, three of the four AD patients were found to exhibit hypometric, OA-like pointing errors (patients 17, 21 and 24), whereas on the obstacle avoidance task only one AD patient was observed to be impaired, showing a lack of implicit obstacle avoidance (patient 20). In combination these tasks imply that all of the AD patients in the sample may exhibit symptoms of OA. This also suggests a potential dissociation between the two tasks, whereby the cognitive mechanisms required to perform each are divergent enough that impairment on one does not imply impairment on the other.

The most striking results to emerge from this series of experiments are those from the pointing task. The results of this experiment strongly suggest OA in three of the four AD patients, with OA-like hypometric pointing errors not evident in any other patient within the sample on this task, with the exception of PCA patient 2. Observing OA-like errors in patient 2 was not surprising given the strong evidence base of OA as a cardinal symptom of PCA (Crutch et al., 2017). However, no prior study has observed OA-like pointing errors in patients with typical AD. The implications of these results are presented and discussed in greater detail below.

6.5.2 Implications and Suggestions for Future Research

Although OA may be a relatively 'covert' symptom, and generally benign in terms of the impact it may have on an individual's activities of daily living and therefore quality of life (with the exception of the most extreme cases), it does not render it a symptom of low research priority. On the contrary, recent ground-breaking evidence suggests that the precuneus – the 'seat' of OA – is the first area in which the pathological cascade associated with the inevitable onset of AD is found, up to two decades before the onset and detection of more typical symptoms of AD (Gordon et al., 2018). The observation of hypometric pointing errors under central fixation (which is highly indicative of OA) in three of the four AD patients in the present sample is potentially a very important finding. Although these results are exploratory, and the sample size small, they certainly warrant further investigation. If a replication study with a greater AD cohort should find similarly striking evidence of OA in AD patients, screening for OA may become a useful tool in the early detection of AD.

Although directed and specific investigations into the presence of OA in AD patients are scarce, there are some clues indicating that dorsal stream dysfunction may be more prevalent in the AD population than previously thought. A systematic review of studies investigating visuospatial dysfunction in dementia between 1960 and 2016 found that tests which target visuospatial functions (particularly visual construction and visual memory) show significant diagnostic and prognostic potential in dementia (Salimi et al., 2018). Indeed, prior research has also indicated that tests of visuospatial abilities may be more accurate than other cognitive tests at differentiating AD from non-AD dementias (Harciarek & Jodzio, 2005; Iachini, Iavarone, Senese, Ruotolo & Ruggiero, 2009; Tiraboschi, Salmon, Hansen, Hofstetter, Thal & Corey-Bloom, 2006).

The finding that impairments in visual memory are particularly diagnostic of dementia is interesting, given the evidence that the posterior parietal lobe is strongly associated with visual working memory retrieval (Berryhill & Olson,

2009; Berryhill, 2012). Bálint's syndrome is comprised of a triad of symptoms associated with parietal, dorsal visual stream damage, namely; OA, oculomotor apraxia, and simultanagnosia (Funayama, Nakagawa & Sunagawa, 2015). Visuospatial working memory has also been observed to be severely impaired in Bálint's syndrome patients, thus it may be that deficits in visual working memory, often observed in dementia patients, are a consequence of dorsal visual stream damage (Funayama, Nakagawa & Sunagawa, 2015; Martín-Loeches, Valdés, Gómez-Jarabo & Rubia, 2009). Visuospatial and visuoattentional functions are reliant on the integrity of the parietal lobe, so it is certainly feasible that the first wave of brain changes in AD which may occur in the precuneus could therefore be detectable by neuropsychological assessments which target dorsal stream functions (Salimi et al., 2018; Gordon et al., 2018). The precuneus has been dubbed 'the mind's eye' due to associations observed between brain activation in this area and visual imagery in memory retrieval tasks – which further points to this area as pivotal for dorsal stream functions (Fletcher et al., 1995).

Visual processing speed has been demonstrated to decrease linearly with normal ageing, with reductions in processing speed the clearest sign of cognitive ageing within the visual domain (Habekost et al., 2013). The 'cognitive slowing' hypothesis assumes that a single factor underlies the cognitive decline observed in normal ageing and, by extension, in Alzheimer's disease (Baddeley, Baddeley, Bucks & Wilcock, 2001). The theory proposes that the speed of basic neural functions declines systematically with age, and thus errors become more frequent due to slower and therefore less effective processing (Baddeley et al., 2001). There is some controversy associated with this single-factor theory, with some researchers suggesting that attentional control is a multi-component process, with some aspects being more vulnerable to change than others (Baddeley et al., 2001; Perry & Hodges, 1999). Perry and Hodges note that, given that the phenomenon of cognitive slowing is well-documented both in normal ageing and in Alzheimer's disease, there is a clear need to disassociate which qualitative changes are a result of healthy ageing, and which are

pathological (Perry & Hodges, 1999; Baddeley et al., 2001). Early researchers ascribed attentional deficits observed in AD to a general, non-specific performance deficit secondary to the more prominent amnesic symptoms (Perry & Hodges, 1999; Posner & Petersen, 1990). However, recent efforts to better understand the human attentional system have led to the current view that deficits in attention in AD may be a consequence of specific damage to parietal attentional networks, and likewise may be related to deficits in activities of daily living often observed for these patients (Perry & Hodges, 1999; Posner & Petersen, 1990).

The theory of visual attention (TVA) is a mathematical model of visual attention which describes the process by which items become selected and encoded into short-term memory (Bundesen, 1990). This model can be used to estimate a set of attentional parameters (including visual processing speed, storage capacity of visual short-term memory, efficiency of attentional control, spatial bias of attention, and the visual perception threshold) in an individual (Habekost, 2015). Bundesen's TVA proposed that simultanagnosia (one of the triad of symptoms which form Bálint's syndrome, indicative of dorsal visual stream damage) may result from a slowing in the rate of visual information processing (Bundesen, 1990; Neitzel et al., 2017; Chechlacz et al., 2012). Another account of simultanagnosia is that it may be the result of a reduced visual short term memory capacity (Neitzel et al., 2017; Chechlacz et al., 2012). There is compelling evidence for deficits in both visual information processing speed and in visual short term memory capacity in patients with AD, as well as patients with mild cognitive impairment (MCI) (which is considered the precursory stage to AD) (Bublak, Redel & Finke, 2006; Habekost & Starrfelt, 2009; Bublak et al., 2011; Janoutová, Šerý, Hosák & Janout, 2015). Thus, simultanagnosia (and therefore, potentially, other dorsal visual stream dysfunctions) may be more prevalent in AD than previously thought. Further elaboration on the evidence for this is presented in Chapter 10.

The results of the present study may therefore be the first step towards a novel cognitive marker for impairment in AD, paving the way towards a new method of screening patients in the prodomal AD phase. Most work on cognitive markers for AD has so far been concerned with memory impairments, specifically episodic and working memory (Carlesimo, Perri & Caltagirone, 2011). The pointing task, after some refinement, could be suited for use in the clinic. Innovations in the use of touchscreen technology in clinical settings are increasingly common, particularly within the dementia population as touchscreen tablets are intuitive and simple to control, and screening using touchscreen technology provides the potential for instant feedback on results for clinicians (Joddrell & Astell, 2016). What is additionally appealing about the potential of an OA screening test such as the pointing task in the present study is that such a measure could feasibly be included as one of the routine tests used by ophthalmologists, thus dramatically increasing the potential for at-risk individuals to be identified and referred for further diagnostic tests.

7. PCA Patient Case Studies

7.0 Introduction

Posterior Cortical Atrophy (PCA) was first identified by Benson and colleagues, who classified it as a distinct subtype of dementia, identifiable by the early visual dysfunction present in these patients (Benson, Davis & Snyder, 1988). The five patients in this original case study were described as developing alexia, agraphia, visual agnosia, and components of Bálint's syndrome (simultanagnosia, optic ataxia and ocular apraxia) and Gerstmann's syndrome (agraphia, acalculia, left-right confusion, and finger agnosia) (Benson et al., 1988). Since this case study, there have been various attempts to phenotype the disease, but as yet no defined clinical diagnostic criteria have been agreed for the disease, although recently there has been an attempt by collaborators to develop a consensus classification framework for PCA (Crutch et al., 2013, 2012; Crutch et al., 2017).

PCA is considered a rare form of dementia, although reports on the disease's prevalence and incidence vary as a function of the diagnostic criteria adopted, with estimates suggesting that PCA may account for up to 5% of AD cases (Crutch et al., 2013, 2012; Lehmann et al., 2011). PCA is most commonly associated with AD pathology (at least 80% of cases), although other etiologies such as corticobasal degeneration, dementia with Lewy bodies, subcortical gliosis, and prion-associated diseases have been reported (Lehmann et al., 2011; Crutch et al., 2013, 2012; Borruat, 2013)

Despite the lack of clear guidelines for the diagnosis of PCA, the disease is generally diagnosed on the basis of visuospatial disturbances in the context of a progressive neurodegenerative syndrome, with an absence of impaired visual acuity or ocular causes which may explain the visual symptoms (Aresi & Giovagnoli, 2009). Patients with PCA typically present in their mid-50s or early 60s with unusual visuoperceptual symptoms with typically preserved episodic

memory and insight into their disease until later stages (Crutch et al., 2017; Borruat, 2013). Common complaints reported by PCA patients include problems with reading and writing, difficulties with driving, identifying letters and recognising and using objects, as well as diminished abilities reaching for and grasping objects (Crutch et al., 2017; Aresi & Giovagnoli, 2009; Rogelet, Delafosse & Destee, 1996).

Visuomotor deficits are strongly associated with presentations of PCA, in fact optic ataxia (a component of Bálint's syndrome) has been suggested as a defining symptom of the disorder – the presence of which is often used as a key factor in the diagnosis of an individual with PCA (Meek, Shelton & Marotta, 2013; Benson, Davis & Snyder, 1988). Other visuomotor deficits often associated with PCA include apraxia and akinesia (Cohen, Burtis, Kwon, Williamson & Heilman, 2010; Aresi & Giovagnoli, 2009). Deficits in visual attention such as visual neglect and simultanagnosia are also frequently reported in addition to visuoperceptual disturbances such as prosopagnosia, alexia, object agnosia, and environmental disorientation (Andrade et al., 2010; Crutch et al., 2013, 2012; Aresi & Giovagnoli, 2009),

This chapter presents six cases of PCA, phenotyped in detail on visuoattentional and visuomotor abilities across Chapters 4, 5, and 6 of this thesis. The aim of this report, therefore, is to provide a summary overview of patients diagnosed with PCA who participated in this study. For in-depth methodological information, as well as elaborative results, please refer to the chapters listed above.

7.1 Patient 1

This 58 year old, right-handed woman with 16 years of education initially presented with PCA, or possible CBD. On clinical examination, this patient was noted to have prominent asymmetrical apraxia and central sensory deficits. This patient received a diagnosis of PCA 2.76 years prior to participating in the present study. This patient exhibited left-sided motor neglect throughout testing, failing to use her left hand when instructed to do so, instead resting it on her lap. Motor weakness was excluded on the basis of reports from her partner that she maintained the ability to use the hand, but seldom did so. This left-sided neglect was further echoed in other tests, where a consistently strong rightward bias was observed, indicative of left visual neglect (bisection and cancellation tasks). This patient was not able to meaningfully interact with a number of the experiments due to the extent of her visual problems, as she failed to respond to any stimuli, or performing at the level of chance (visual search, Navon and Posner tasks). In confrontation testing, this patient appeared to 'progress' from left-sided motor neglect in the free vision condition to an inability to initiate a movement with either hand under central fixation, possibly indicative of severe optic ataxia (OA). This patient also exhibited behaviour consistent with presentations of simultanagnosia (SA) (cancellation task, gap bisection, confrontation by extinction). Qualitative insights gained from this patient during screening testing appear to offer further support to the presence of SA in this individual. The patient stated that "the more you see, you can't pick out features", and "when there are two things I can't tell where the information goes", when completing the BORB object decision task. She also described her visual experience as "once you see it, you can't go back on it, your brain is full and you can't go back to the start". Example stimuli from the BORB object decision task are presented in Figure 7.1, below, along with the patient's responses. These illustrate the consistent failure to form a complete percept of the images by this patient, and her experience of being unable to disambiguate features, or indeed to perceive more than one feature following initial inspection.

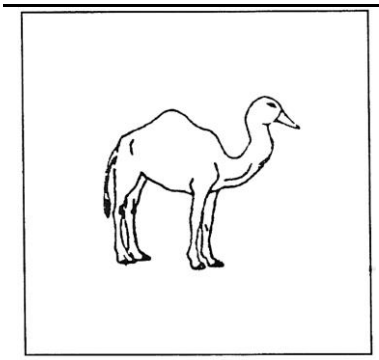
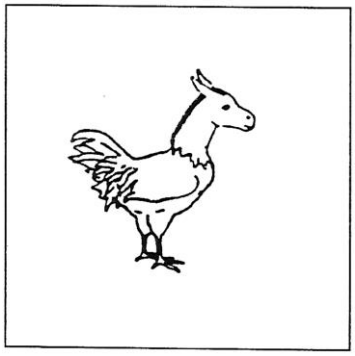
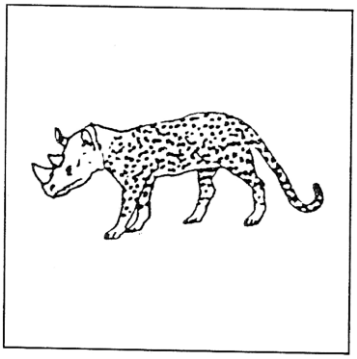
Image	Target [Correct Response]	Patient Quote [Final Response]
	Camel/Duck [unreal]	"I don't think it's real, I don't know why". [unreal]
	Donkey/Cockerel [unreal]	"I think it's a chicken". [real]
	Leopard/Rhino [unreal]	"Cheetah? I'll go for real". [real]

Figure 7.1: BORB Object Decision Task (Subtest 10) Example Responses (PCA Patient 1).

The most recent brain scan available for this individual was evaluated by a consultant neurologist (AW, see Chapter 8 for further details). The posterior atrophy was categorized as a Koedam score of 2. The posterior atrophy visual rating scale (referred to as the Koedam scale within this thesis) measures the degree of posterior atrophy on a rating scale from 0 (no atrophy) to 3 (severe atrophy) (see Chapter 8 for further elaboration on this scale) (Koedam et al., 2011). Note that the scan on which this score was based was completed 4 years prior to assessment in the present study, thus this score may have been more

progressed at the time of testing. Certainly, the visuoattentional symptoms exhibited by this patient imply significant posterior parietal atrophy.

7.2 Patient 2

This 58 year old, left-handed woman with 9 years of education initially presented with sleeping problems as a consequence of 'voices in her head', leg pain and occasional numbness, as well as decreased appetite, verbal working memory deficits, visuospatial dysfunctions, and spelling and calculation deficits . This patient received a diagnosis of PCA 3.35 years prior to participating in the present study. This patient exhibited symptoms which may be consistent with right-sided visual neglect (Posner and obstacle avoidance tasks). Qualitatively, throughout the process of testing this individual, it was noted that she often held her head tilted rightward, which may also be a consequence of right-sided neglect (Taylor, Ashburn & Ward, 1994). It was also observed through the course of testing that this patient found it very hard to detect edges and was very unsteady on her feet, and thus struggled to walk without assistance, to use stairs, or to sit on a chair without guidance or without first feeling for the margins of the chair with her hands. These deficits could be related to an apperceptive issue with figure-ground segmentation. This patient also exhibited symptoms of a possible postural neglect disorder, supported by the observation of the head tilt towards the (suspected) neglected side of space (Pérennou, 2006). The postural neglect concept has been described as an under-integration of sensory-motor information from the contralesional hemispace, resulting in a postural imbalance towards the neglected side (Pérennou et al., 2000). Bilateral OA was also evident on confrontation testing, further supported by a lack of implicit avoidance of obstacles (possibly symptomatic of OA). OA-like pointing errors were strongly evident on the pointing task by the increasingly hypometric errors with increasing target eccentricity (see Figure 7.2, below).

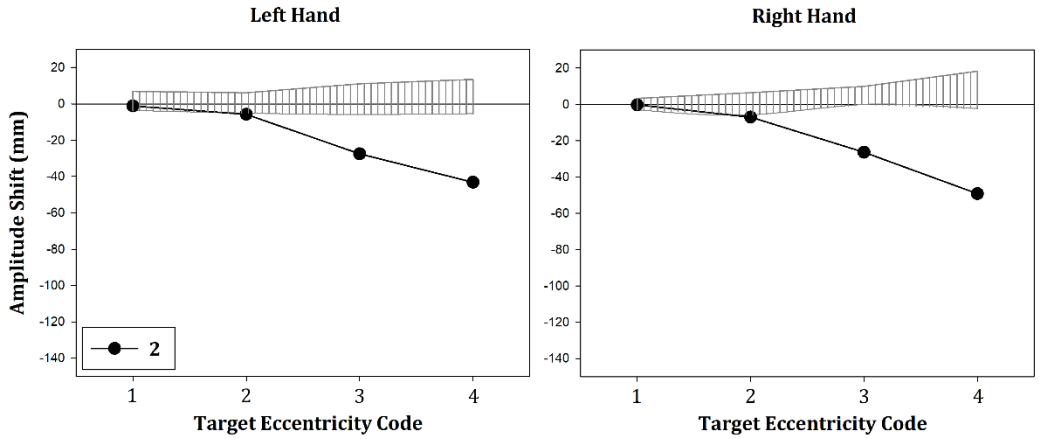


Figure 7.2: Amplitude Shift Between Free Vision and Central Fixation Conditions.
Note: Shaded area represents normal performance.

This patient failed to end the experiment in the invisible cancellation task, instead continuing to search for targets in the visual array until the task timed out. This is suggestive of a deficit in visuospatial working memory.

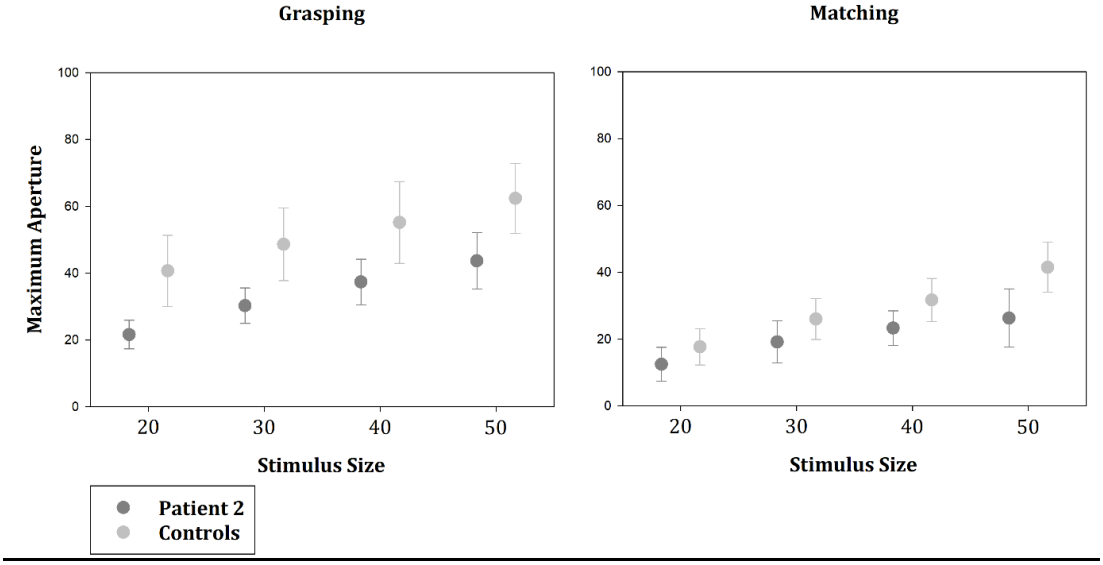


Figure 7.3: Mean Maximum Aperture for Grasping and Matching with Standard Deviations (Patient 2)
Note: 'Maximum Aperture' is MGA for grasping task, MAP for matching task.

Perceptual deficits were also observed on the matching task for this individual, whereby her estimate of the block's size was abnormally small. The regression slope gained between maximum aperture and block size differed significantly

from the regression slope gained from age- and sex-matched controls for the matching task, further demonstrating the abnormal association between block size and MAP for this individual (see Figure 7.3, above). This individual's MGA appears under-scaled for the grasping task also, however the regression slope for this individual did not differ significantly from that of controls for the grasping task. This patient was given a Koedam score of 0 from a scan completed during the same year as testing. This score demonstrates a surprising lack of posterior atrophy, given the relatively pronounced posterior symptoms exhibited by this individual (optic ataxia, neglect, visuospatial working memory and perceptual deficits).

7.3 Patient 3

Patient 3 was a 65 year old, right-handed woman with approximately 9 years of education. This participant had to withdraw from the study during the screening phase due to a family bereavement. Thus, only very limited data are available for report.

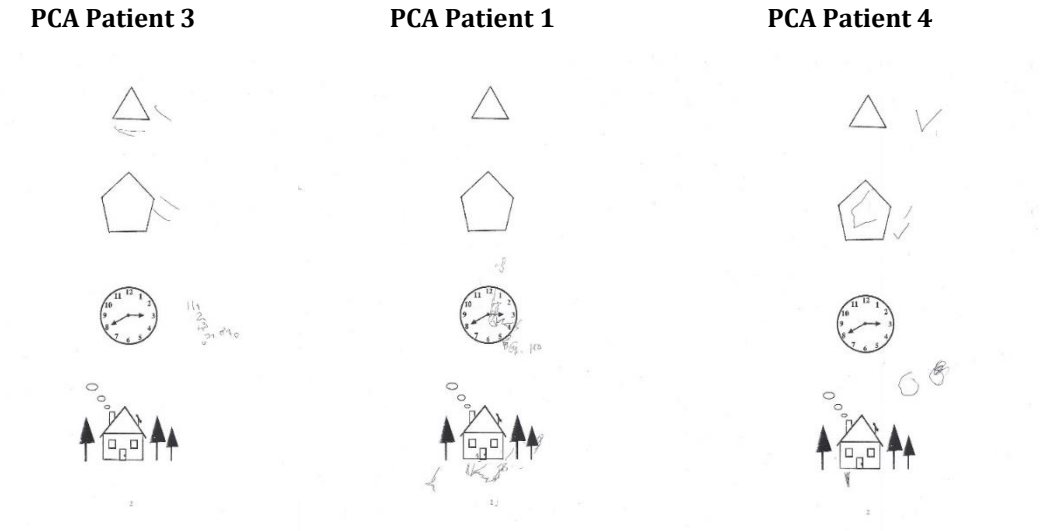


Figure 7.4: BORB 1 – Figure Copy (PCA Patient 3)

Visual neglect was suspected in this patient as a consequence of her impaired performance on the BORB 1 figure copy test. Certainly, her performance on this test appeared similar to that of PCA patients 1 and 4, both of whom exhibited symptoms of visual and motor neglect throughout testing (see Figure 7.4, above, for comparison). This patient was not able to complete BORB Subtest 6, but was found to be impaired on both paired non-overlapping and paired overlapping letters, only getting two letters correct in the latter task, and making frequent errors in the non-overlapping task. Even with such limited data, visual deficits were clearly present in this individual.

7.4 Patient 4

This 51 year old, right-handed woman with 12 years of education initially presented with difficulty driving, having stopped approximately 8 months prior to her initial clinic assessment. This patient also demonstrated problems with motor planning and execution (praxis), tested by means of gesture imitation (worse on the right-hand side), as well as repetitiveness in conversations and reduced confidence. Severe memory and visuospatial deficits were observed on the ACE-III. This patient received a diagnosis of PCA 1.77 years prior to participating in the present study. A proxy report provided by her husband at the time of testing noted that she had been increasingly struggling with symptoms of anxiety and depression. On screening, this patient demonstrated evidence of closing-in behaviour (CIB), which may be symptomatic of visuo-constructional apraxia (see Figure 7.5, plot a, below, for Patient 4's response on the BORB figure copy test and plot b, for this patients M-LAST responses, both demonstrating CIB).

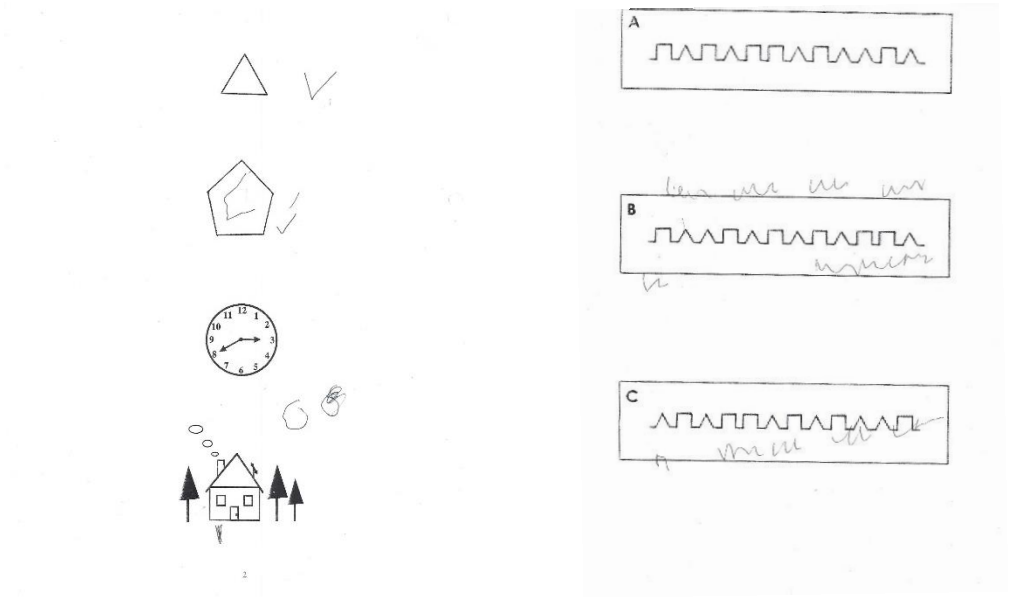


Figure 7.5: a) BORB 1 – Figure Copy (PCA Patient 4) **b) M-LAST Task (PCA Patient 4)**

Left-sided motor neglect was observed in this patient, whereby she demonstrated spontaneous underuse of her left hand – failing to use this hand when instructed, and holding her left arm close to her body. Left-sided visual neglect was also evident on the cancellation tasks, as were suspected deficits in visuospatial working memory (both for visible and invisible). Qualitative observations taken during the screening phase noted that this individual appeared to favour stimuli on the right side of space, for example, consistently selecting the right-sided item when two items were presented side-by-side (BORB Subtest 7), possibly additionally indicative of left-sided visual neglect. This patient was untestable on the visual search tasks due to her turning her head leftwards and leaning back, out of the head rest, which may indicate postural neglect – similar to patient 2. Simultanagnosia was observed on the gap bisection task, with the patient failing to detect the left endpoints of stimuli (see Figure 7.6, below).

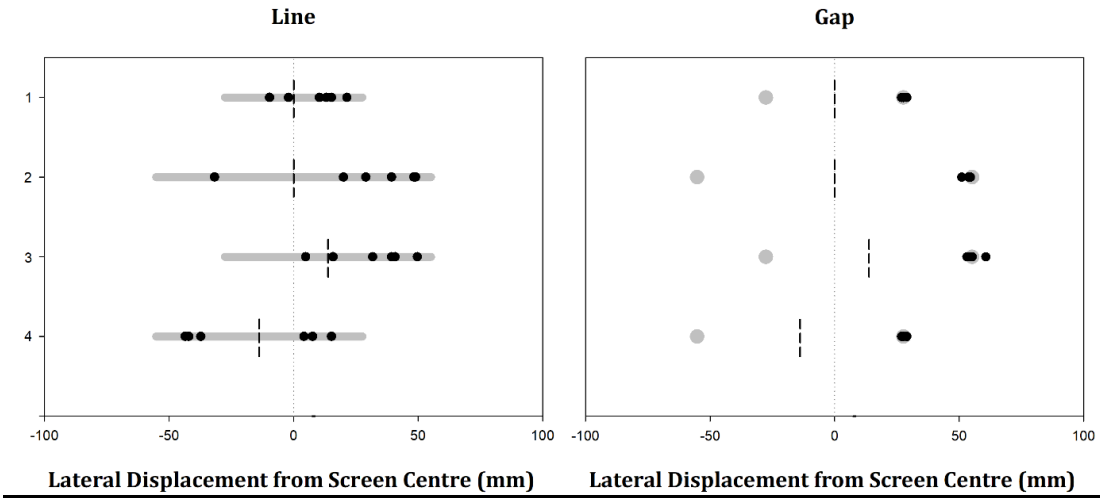


Figure 7.6: Individual Response Data for Line and Gap Bisection (Patient 4)
Note: Dotted grey line represents screen midpoint, dashed black line represents true stimulus midpoint.

Dramatic magnetic misreaching was observed under central fixation for this individual – strongly suggestive of OA – whereby she touched the experimenter's nose (her point of fixation) rather than reaching peripherally to touch targets (OA by confrontation test). Most dramatically, this patient was unable to complete a number of experiments as she could not locate the computer screen in space, despite the fact the screen was positioned directly in front of her (visual search, Posner, and Navon). Interestingly, this patient was given a Koedam score of 1 (scan completed 2 years prior to testing). It seems likely, given the progressive nature of dementia as well as the severe visual impairments observed for this patient as well as the specific visuoattentional and visuomotor deficits observed, that this score may have progressed since the time of the scan.

7.5 Patient 5

This 67 year old, right-handed man with 11 years of education initially presented with complaints of a gradual decline in memory and concentration. He reported feeling as though 'brain and hand are not connected'. This patient also presented with deficits in writing and difficulties dressing. He was found to

be repetitive in conversation and had difficulties telling the time as well as poor balance and low mood. No REM sleep disorder or tremor were detected and no hallucinations were reported, however the patient described a feeling of someone being just behind him and that he possibly saw the 'outline of a person'. This patient received a diagnosis of PCA 2.06 years prior to participating in the present study. The most striking results from this individual were those of spontaneous, induced, left-sided motor neglect under central fixation on confrontation testing. These results suggest that the increased attentional demands of the central fixation task, compared to free vision, led to a pathological deficit in attention manifest as underuse of the left hand – even with repeated prompting. A rightward bias was observed on the invisible cancellation task, suggestive of left-sided visual neglect (therefore also manifest under the increased attentional demands of the invisible compared with the visible cancellation task, as the invisible cancellation task additionally requires the recruitment of visuospatial working memory processes). There was also evidence of left-sided visual extinction for this individual (extinction by confrontation test).

Abnormalities of visual search were noted, as well as an impaired overview of the visual array and possible deficits in visuospatial working memory (pop-out and conjunction visual search, and visible and invisible cancellation tasks). Deficits of attention were observed indicating abnormalities of visual processing as well as implicit avoidance of obstacles (Posner and obstacle avoidance tasks). This patient required repeated prompting on task instructions on both screening and laboratory based assessments, further suggestive of general attentional deficits. The patient reported that around 6 months prior to participation in the study (approximately 1.5 years post-diagnosis) his visual problems had progressed; he stated that he now had difficulty seeing things in front of him as well as problems recognising common objects (such as an eraser). His wife noted that he could no longer use a knife and fork, and corroborated his report of generally worsening visual problems, as well as noting what she described as stronger symptoms of dementia generally

(presumed to be deficits in memory). Thus, a caveat to the interpretation of visual symptoms reported above for this individual would be that, in the context of general visual deficits, interpretation of specific deficits from specific assessments can be problematic. It was not possible to generate a Koedam score for this individual because the available brain images were of too poor a resolution to determine region-specific atrophy.

7.6 Patient 6

This 69 year old, right-handed man with approximately 12 years of education initially presented with probable AD. A history was taken by proxy from his wife. She reported memory problems as well as word-finding difficulties. His writing had become affected, and his spelling had also deteriorated. Occasional involuntary jerking movements during the day time were noted. On examination, symptoms suggestive of marked praxis difficulties were found (deficits in gesture imitation). This patient received a diagnosis of PCA 0.72 years prior to participating in the present study. During the screening testing, this patient stated that he was still able to pursue his interests in literature and language and was in the process of teaching himself Italian, but he was aware that he struggled to maintain concentration at times and had some problems with memory in his everyday life. At the point of laboratory testing (6 months later), this individual struggled to maintain concentration and would require fairly regular prompting on the task rules, finding it particularly difficult to complete tasks which required rule switching (such as the pointing task). This patient was notably quite capable visually, particularly when compared with other PCA patients within the sample, and often performed at the level of controls (extinction by confrontation, pop-out visual search, line and gap bisection, visible cancellation, and Posner tasks). However, very clear CIB was observed during screening (BORB 1 figure copy and modified Luria alternating square and triangles (M-LAST) (see Figure 7.7, below, for details). Errors were observed under confrontation testing, however these were not congruent with

an OA-like pattern and were therefore interpreted as being related to other behavioural factors. This individual also demonstrated perfect accuracy on extinction testing.

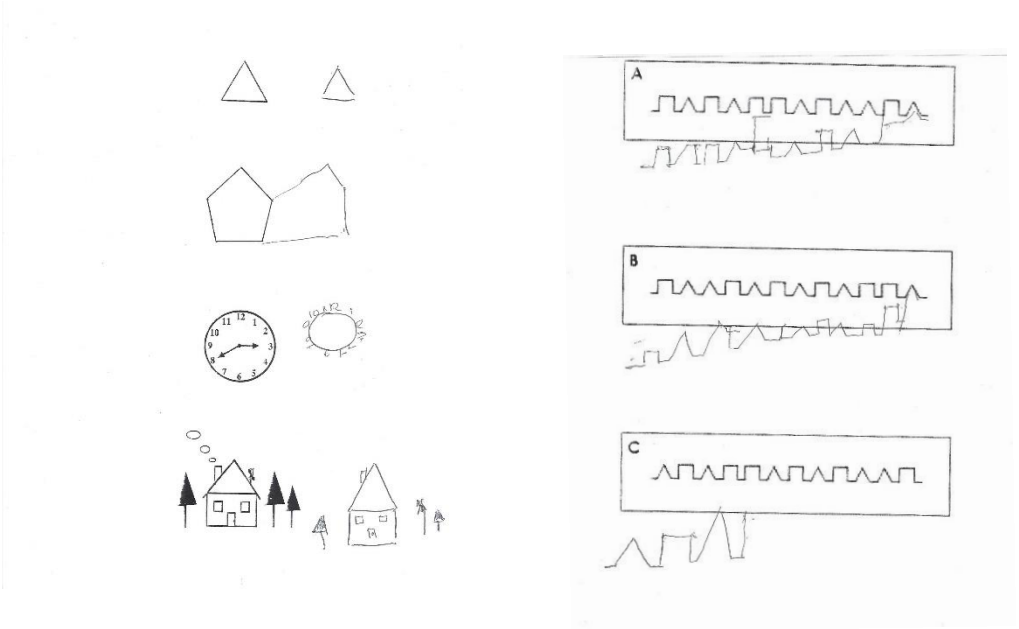


Figure 7.7: a) BORB 1 – Figure Copy (PCA Patient 6) b) M-LAST Task (PCA Patient 6)

This individual appeared to show some deficits when confronted with more attentionally-demanding conditions of various tasks (conjunction visual search, invisible cancellation). Responses on the obstacle avoidance task had a strong bias towards the COP, but these fell within the limits of normality (see Figure 7.8, below).

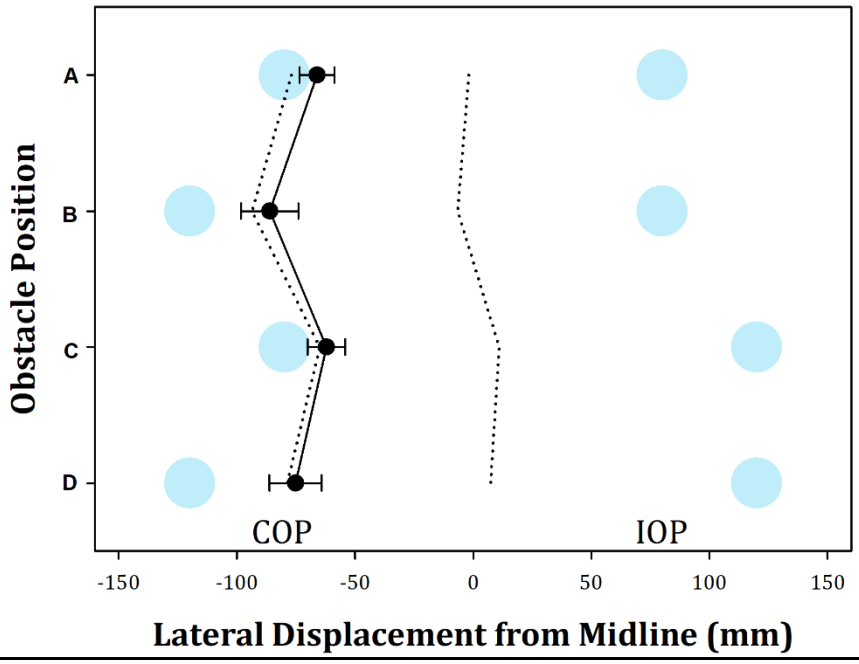


Figure 7.8: Median Transection Points (with standard deviation) (Patient 6)
Key: COP = contralateral obstacle position, IOP = ipsilateral obstacle position, · · · · · represents boundaries of normal performance.
Note: Blue circles represent position of stimuli for each obstacle position code (A-D).

Thus, this individual presented with some generalised deficits in attention with no evidence of any lateralised bias (neglect), simultanagnosia, or OA. The Koedam score generated for this individual was 2 (based on a scan completed 1 year prior to testing). It is rather surprising that this individual demonstrated such preservation of visuoattentional and visuomotor abilities, given the advanced state of atrophy of the posterior parietal regions. Qualitatively, this patient's difficulties with maintaining attention appeared to have progressed considerably in the 6 months between screening and laboratory-based testing.

7.7 General Discussion

The level of impairment between patients in this study varied considerably, with the most impaired patients (patients 2 and 4) appearing at times to be almost functionally blind, particularly evident when they were observed attempting to navigate their environment, peripheral to testing. Other patients

were less impaired overall (patient 5 and 6), but were observed to have deteriorated in their abilities in the relatively short time between the initial screening and subsequent laboratory-based testing, suggesting a fairly rapid time course of progression. Clearly, between-subject differences observed between patients will be a function of many factors such as the pathological cause of PCA, time since diagnosis, level of disease progression, degree of posterior parietal involvement, and indeed hemispheric asymmetry of atrophy. Koedam scale scores provided an estimate of the degree of posterior atrophy for each individual, however, many of the scores reported in the present study were based on brain scans which had been conducted years prior to testing, and thus only deliver a rather coarse estimate of cortical damage. In one case (patient 6), the Koedam score indicated an advanced level of atrophy, whereas behaviourally this patient performed at the level of controls on many tasks.

It is possible that some of the differences in symptom presentation between patients in the present sample may also be accounted for by different subtypes of PCA, namely ventral or dorsal presentations – a distinction first proposed by McMonagle and colleagues (McMonagle, Deering, Berliner & Kertesz, 2006; Migliaccio et al., 2012). These subtypes are based on the dual stream hypothesis of visual processing whereby the ventral stream processes object identity and recognition ("what") information, and the dorsal stream is concerned with processing spatial location ("where") information (Goodale & Milner 1992; Milner & Goodale, 2008). The ventral subtype of PCA is thus characterised by deficits in visual object processing (manifest as problems with object, face, colour, or written word recognition), whereas the dorsal subtype is typified by problems with the processing of spatial location (such as spatial awareness and reaching movements) (Migliaccio et al., 2012).

Prior studies investigating these purportedly discrete subtypes of PCA note that the dorsal presentation is more common, with the ventral presentation reported only rarely (Tsai, Teng, Lui & Mendez, 2011; Caine, 2010; Spehl et al., 2015; Ross et al., 1996). Indeed, even within the limited sample in the present

study, two distinct groups form upon close examination of the symptom profiles. Namely, three of the patients in the sample presented with strongly dorsal-stream associated symptoms (such as neglect, OA, and SA) (patients 1, 2, and 4), whereas two patients showed inconsistent (such as the spontaneous induced left-neglect observed in patient 5) or absent symptoms of dorsal stream dysfunction (patient 6) – with more prominent symptoms relating to general deficits in attention such as deficits in attentional shifting (observed for patient 5 on the Posner task), problems concentrating, difficulties with task shifting (both patients 5 and 6), as well as CIB (patient 6).

Neurodegenerative diseases do not progress according to functional boundaries, therefore subtypes of PCA will likely present with mixed ventral and dorsal symptomology, with the subtype classification referring to the visual stream which has the greater degree of damage. Thus it may be more accurate to say that patients are 'more ventral' or 'more dorsal' on presentation. It therefore seems feasible that the two clusters which emerge from this study may represent patients with symptoms suggesting a more dorsal profile (patients 1, 2, and 4) and those with a (presumed) more ventral profile (patients 5 and 6). However, the tasks in the present study were designed to challenge visuoattentional and visuomotor abilities, which are generally accepted to be dorsal stream functions, therefore in lieu of more thorough testing on ventral stream functions (beyond the very limited object perception tests which formed part of the screening battery, on which neither patient appeared to be impaired), such a distinction between the clusters is made only very speculatively.

Patients presenting with profound visual deficits will perform at a deficit on any visually-based task, regardless of the cognitive domain which the task is targeted towards. This is a fundamental limitation of the present study, and indeed any study investigating this disease, as attempting to better understand

the visual symptom profile of PCA using visually-based tasks is inherently limited and confounded by the visual symptoms themselves. For example, the knock-on effect of having visual symptom 'A' may be an artificially increased profile of deficit on tests which are designed to target other visual symptoms or indeed other cognitive modalities entirely; the presence of visual symptom 'A' will inevitably cause the individual to perform at a deficit on any visually-based test. Patient 4 in the present sample, for example, presented with strong evidence of left-sided visual neglect. This left-sided visual neglect may have had a causal or additive effect on the deficit observed on tasks included in the study which were presented visually (but not targeted at visual abilities) such as the TROG-1 and the test for alexia. Acknowledgement of the confounding effects of visual symptoms is therefore important when interpreting symptoms in case studies of PCA.

8. Brain Morphology

8.0 Introduction

8.0.1 Diagnosing Dementia & Assessment of Atrophy

Clinical features of PCA – including visuospatial and visuoperceptual impairments, Bálint's syndrome, Gerstmann's syndrome, and alexia, among others – generally differ from those of typical Alzheimer's disease (AD) until later in the course of the disease, where features of PCA and typical AD tend to converge (Singh et al., 2015).

Pathologically, PCA has been attributed to a number of causes which are typically determined using biomarkers found in cerebrospinal fluid (CSF). Histopathological examination of brain tissue by means of a biopsy would provide a more accurate diagnosis, however such tests are generally contraindicted for AD due to the high risk to benefit ratio (Beach, Monsell, Phuillips & Kukull, 2012). As such, in-vivo CSF biomarkers are typically used in clinical practice, although measures of all biomarkers currently studied demonstrate considerable overlap between dementia types and indeed within the healthy elderly population (Beach et al., 2012). Therefore, autopsy continues to serve as the 'gold standard' for accurate pathological diagnosis of neurodegenerative diseases like AD (Beach et al., 2012).

The most common pathological cause of PCA is AD, in which neuritic plaques and neurofibrillary tangles are observed as a consequence of extracellular deposition of beta-amyloid (Aβ) peptide and intraneuronal accumulations of hyperphosphorylated tau (P-τ) protein (Forlenza et al., 2015; Lista et al., 2014). The CSF signature of AD (when compared with cognitively normal elderly individuals) is decreased concentrations of Aβ (by an average of 50%), with increased total-τ and P-τ (300% and 200%, respectively). These biomarkers, in

combination, have a sensitivity and specificity between 85-95% for the diagnosis of AD, both at prodromal and dementia stages of the disease (Forlenza et al., 2015). Other pathological causes of PCA include corticobasal degeneration (CBD), Lewy Body dementia (LBD), and Creutzfeldt-Jakob disease (CJD). In contrast to AD, patients with CJD pathology demonstrate extremely high total-τ with relatively normal P-τ (Schoonenboom et al., 2012). However, a large degree of overlap between CSF biomarker profiles has been observed between AD and other dementia types including CBD and LBD, therefore specificity of these biomarkers is moderate (Schoonenboom et al., 2012). This is generally attributed to the fact that many dementias are discovered to have a mixed pathology at autopsy; pure forms of AD or other types of dementia are considered a minority within the whole spectrum of dementia (Schoonenboom et al., 2012).

Typically, therefore, a diagnosis will be achieved using a combination of biomarkers, clinical features and structural neuroimaging. Given that dementia can be produced by a large number of pathological causes (see Chapter 1 for further details), and in light of the fact that these processes can be difficult to distinguish between clinically – particularly in the early stages of disease development – neuroimaging is increasingly used to aid in diagnosis (Scheltens, Fox, Barkhof & De Carli, 2002). Blood screening tests may identify some rare (but treatable) causes of dementia, including metabolic disorders, vitamin B12 deficiency, and central nervous system infections such as neurosyphilis and HIV (Tripathi & Vibha, 2009; Scheltens et al., 2002). However, the yield from these tests is low (Scheltens et al., 2002). Thus, neuroimaging is a highly informative tool for the differential diagnosis of dementia disorders.

Figure 8.1, below, presents a theoretical model of cognitive and biological markers of AD and the time frames in which these markers are most sensitive.

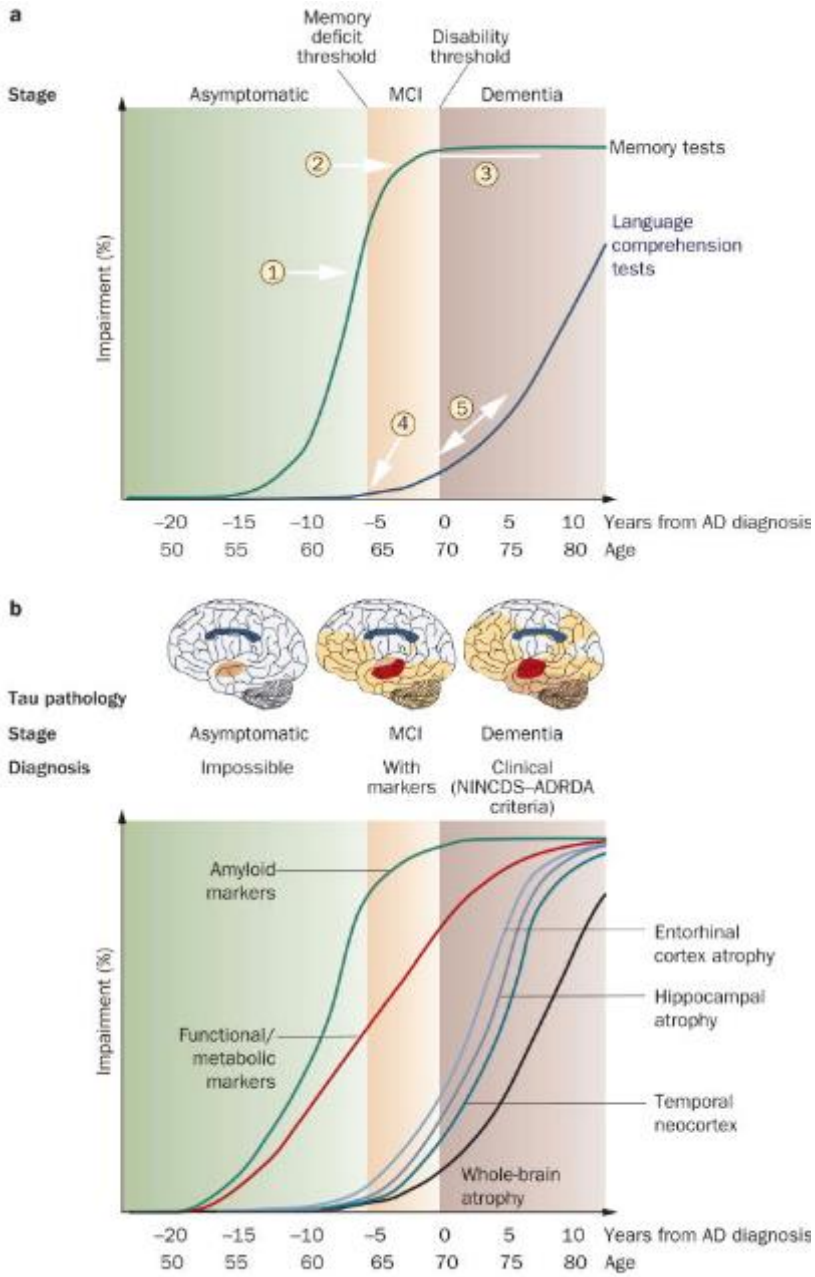


Figure 8.1: Theoretical Model of Cognitive and Biological Markers of Alzheimer's Disease (from Frisoni et al., 2010).

Key: a)(1) Memory tests may be sensitive to early changes but reach the maximal level of impairment rapidly, but (2) may be useful for diagnosis at the MCI stage but (3) less useful for tracking later disease progression. (4) Verbal comprehension tests start to change later in the disease course, and are of limited use diagnostically. b) Amyloid markers (CSF amyloid-β_{42} and PET amyloid tracer uptake) represent the earliest detectable changes in the AD course, but have plateaued by the MCI stage. Functional and metabolic markers detected by task-dependent activation on fMRI and F-flurodeoxyglucose PET are abnormal by MCI stage, and continue to change well into the dementia stage. Structural changes come later, following a temporal pattern mirroring tau pathology deposition.

The model demonstrates that some markers are sensitive to disease state and are therefore useful for diagnosis (such as memory tests, amyloid and metabolic markers – which are sensitive to early changes but reach a plateau after the disease has reached maximal impairment on that marker) whereas others are more sensitive to disease progression, like language comprehension tests and structural imaging measures (Frisoni et al., 2010). Imaging is included in the diagnostic criteria of the most prevalent non-AD dementias, e.g. vascular dementia, frontotemporal dementia (FTD), LBD and CJD – which demonstrates the value of this technique for differential diagnosis (Frisoni, Fox, Jack, Scheltens & Thompson, 2010).

The structural imaging technique most widely used in clinical research and commonly used in clinical practice is the T1-weighted MRI (Valkanova & Ebmeier, 2014). MRI-based measures of atrophy are considered valid measures of both disease state and disease progression (Frisoni et al., 2010). Progressive brain atrophy appears to be inexorably associated with neurodegeneration, and the location of tissue loss is well correlated to cognitive deficits (Frisoni et al., 2010).

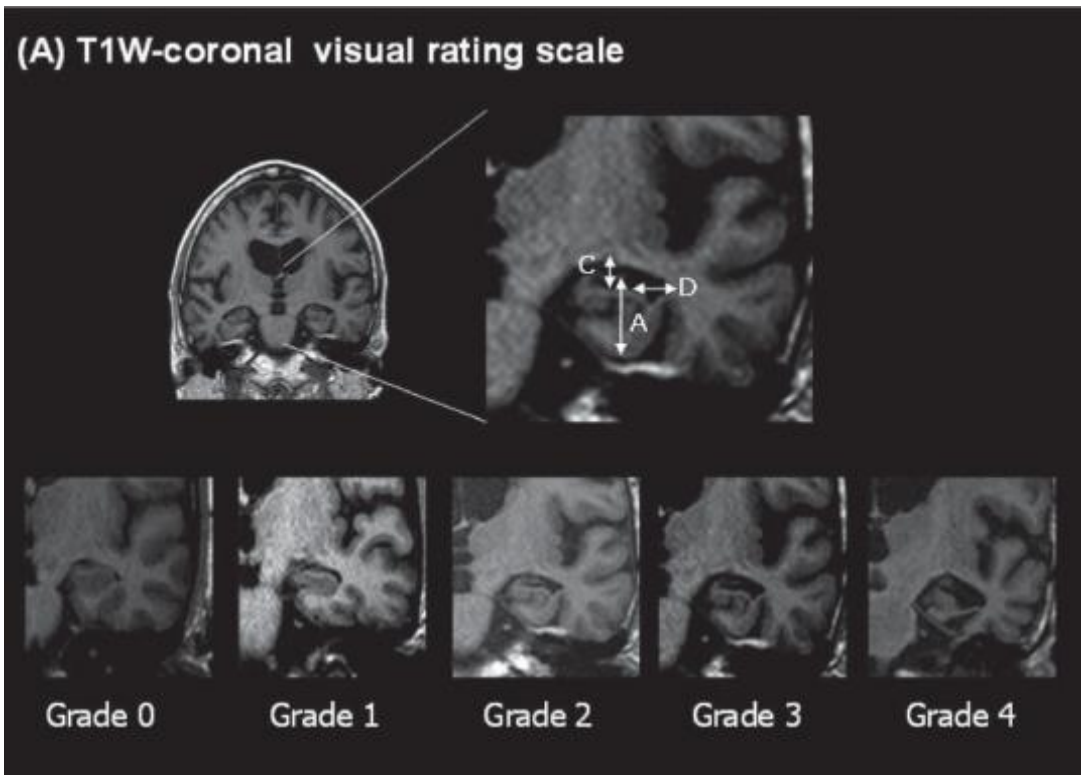


Figure 8.2: MTA Visual Rating Scale from 0-4 (adapted from Kim et al., 2014).
Key: (for top right image) A) Height of hippocampal formation, C) vertical width of the choroid fissure, D) width of the temporal horn.

In clinical practice a visual assessment of MRI scans is used most often to quantify atrophy (Valkanova & Ebmeier, 2014). Indeed, visual inspection has been demonstrated to differentiate between mild AD and normal ageing with a sensitivity and specificity of 80-85% (Scheltens et al., 1992; Duara et al., 2008). Visual assessment has some advantages over quantitative volumetric analysis as it is less time intensive and easier to apply in clinical practice (Kim et al., 2014). Rating scales are used to quantify visual assessment of atrophy in given brain regions.

The Scheltens' MTA rating scale is commonly used in the diagnosis of AD and is concerned with atrophy of the structures of the hippocampus (Valkanova & Ebmeier, 2014). The hippocampus and adjacent structures are crucial to memory, therefore their bilateral atrophy leads to losses in this cognitive domain, characteristic of AD (Scheltens et al., 1992). The MTA assesses

hippocampal atrophy (according to the width of the choroid fissure, width of the temporal horn, and height of the hippocampus) on a severity scale from 0-4 (see Figure 8.2, above) (Valkanova & Ebmeier, 2014).

Perhaps most relevant to the pattern of atrophy typically observed in PCA is the visual rating scale developed by Koedam and colleagues, which classifies posterior cortical atrophy on a scale from 0-3 (see Figure 8.3, below) (Koedam et al., 2011).

Saggital Orientation Axial Orientation Coronal Orientation

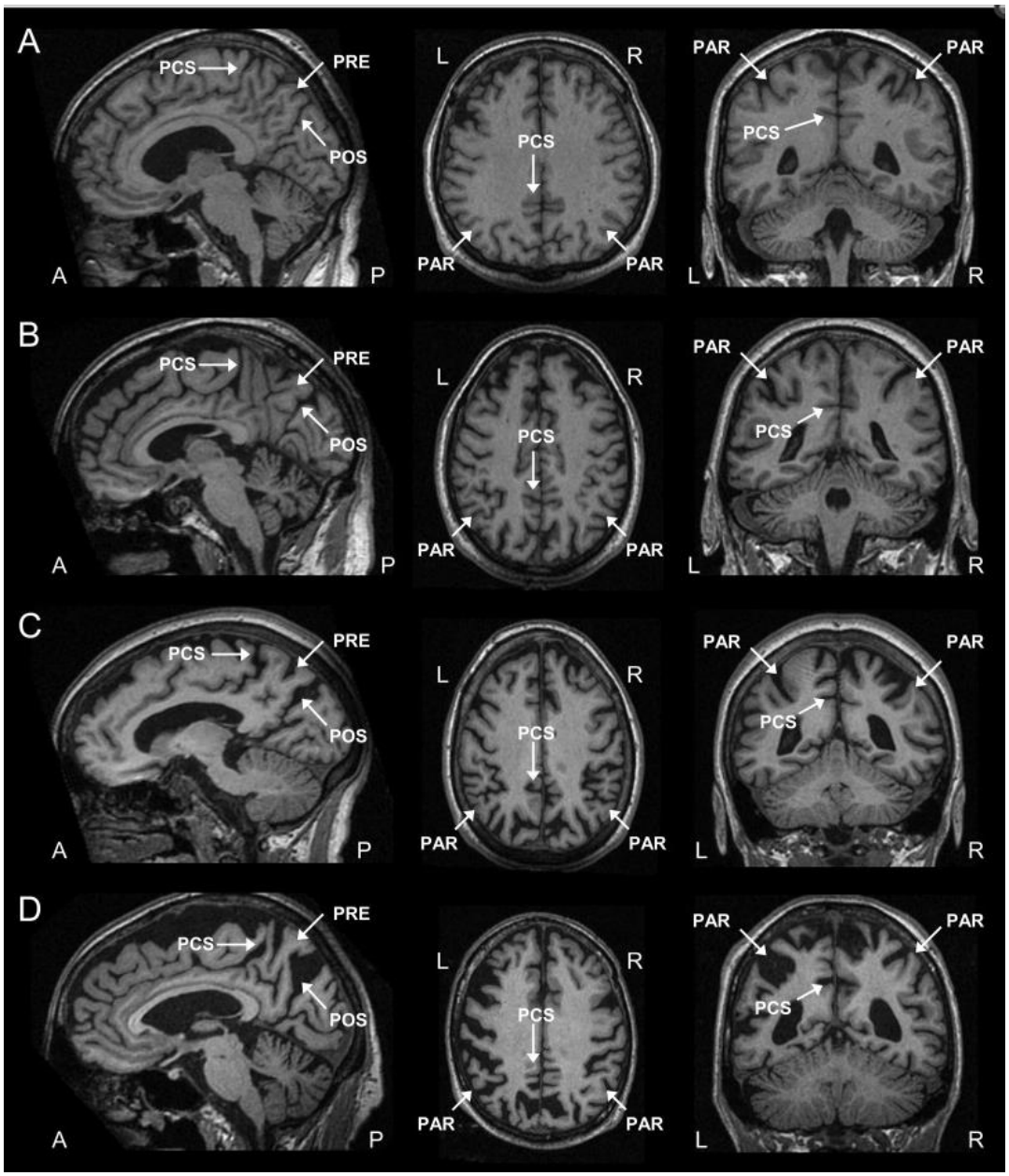


Figure 8.3: Koedam Visual Rating Scale for the Posterior Brain Regions (from Lehmann et al., 2012).
Key: A = grade 0, no atrophy, B = grade 1, minimal atrophy. C = grade 2, moderate atrophy, D = grade 3, severe atrophy.
PAR = parietal lobe, PCS = posterior cingulate sulcus, POS = parieto-occipital sulcus, PRE = precuneus.

This posterior atrophy rating scale (referred to hereafter as the Koedam scale) classifies atrophy using distinct anatomical landmarks in three different orientations, defined below:

1. Saggital orientation: widening of the posterior cingulate- and parieto-occipital sulcus, and atrophy of the precuneus on left and right by considering paramedian-sagittal images.
2. Axial orientation: widening of the posterior cingulate sulcus and sulcal dilatation in parietal lobes on axial images.
3. Coronal orientation: widening of the posterior cingulate sulcus and parietal lobes on coronal images.

   (from Koedam et al., 2011)

The Koedam scale was found to be a reliable measure of parietal grey matter atrophy in a validation study where the specificity of the scale was compared to that obtained from more detailed volumetric voxel-based morphometry analysis (Möller et al., 2014). The results indicated that the Koedam scale discriminated well between atrophy (PCA-1 and PCA-2) and no atrophy (PCA-0), and therefore can be considered a useful tool for rapid assessment of parietal atrophy (Möller et al., 2014).

8.0.2 Differential Imaging Features of Posterior Cortical Atrophy

Neuroimaging of PCA patients typically reveals bilateral grey matter atrophy and hypometabolism in the primary visual cortex, as well as parieto-occipital and occipito-temporal cortices (Aresi & Giovagnoli, 2009; Mendez, Ghajarania & Perryman, 2002; Beh et al., 2015; Whitwell et al., 2007). Typically patients with PCA demonstrate distinct, predominantly right-sided, hypometabolic regions from the primary visual cortex through the dorsal visual association cortex to the parietal lobe (see Figure 8.4, below) (Spehl et al., 2015; Lehmann et al., 2011; Millington, James-Galton, Da Silva, Plant & Bridge, 2017; Crutch et al., 2012). Symmertical areas of hypometabolism are also commonly observed in the region of the frontal eye field (FEF), which is an area considered vital for the generation of normal, voluntary eye movements and therefore implicated in presentations of oculomotor apraxia in PCA patients (Nestor et al., 2003; Crutch

et al., 2012; Cerami et al., 2015). Cortical loss may also extend superiorly and anteriorly across primary sensory and motor cortices, with sparing of the anterior temporal and prefrontal cortex (Whitwell et al., 2007).

Using voxel-based morphometry, PCA patients show fewer pathological changes compared to typical AD to the prefrontal cortex and hippocampus, but greater densities of senile plaques and neurofibrillary tangles in the occipital lobe, parietal lobe and occipitotemporal junction (Lehmann et al., 2011). Figure 8.4, below, presents average cortical thickness profiles of 48 patients with PCA and 30 with typical AD, as well as data from 50 age- and sex-matched healthy controls (Lehmann et al., 2011). From this figure the preferential atrophy of the posterior parieto-occipital lobe in PCA when compared with typical AD (Figure 8.4, image C) is particularly evident, as is the greater comparative hippocampal volume.

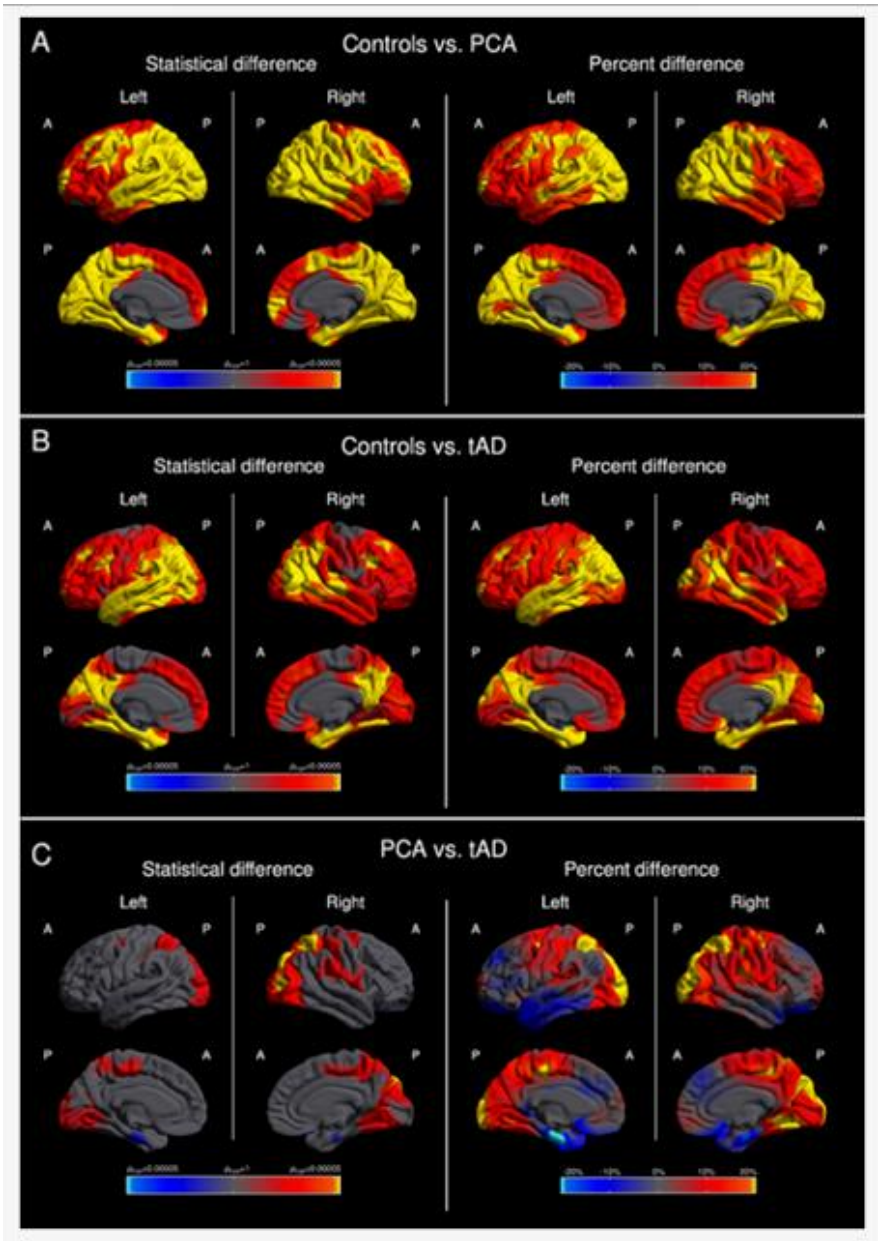


Figure 8.4: Regional variation of cortical thickness in (A) PCA compared with controls, (B) typical AD compared with controls, (C) PCA compared with typical AD, for the left and right hemisphere.
The colour scale for statistical difference represents FDR-corrected p values at a 0.05 significance level, whereas the colour bar for percent difference represents magnitude of cortical thickness difference. Red and yellow (positive values) represent lower cortical thickness in (A) PCA compared with controls, (B) typical AD compared with controls, (C) PCA compared with typical AD, whereas dark and light blue (negative values) represent greater cortical thickness. L: left hemisphere, R: right hemisphere, A: anterior, P: posterior. (from Lehmann et al., 2011).

The observation that PCA patients are often reported as demonstrating greater grey matter loss in the right hemisphere suggests that there may be a systematic bias towards diagnosing patients with right hemisphere damage as

having PCA (Millington, James-Galton, Da Silva, Plant & Bridge, 2017; Meek, Locheed, Lawrence-Dewar, Shelton & Marotta, 2013). This hypothesis is supported by Ryan and colleagues who state that patients with predominantly right hemisphere deficits affecting their vision are more likely to be diagnosed by a cognitive neurologist as having PCA than those patients with predominantly left hemisphere deficits (like progressive apraxia or dysgraphia) (Ryan et al., 2014). Crutch and colleagues additionally acknowledged that the asymmetric atrophy patterns reported in several studies of PCA may be a consequence of selection biases, with patients showing prominent visual disturbances being more likely to be diagnosed with PCA and therefore recruited to studies on the disease (Crutch et al., 2012). As yet no clear diagnostic criteria are available for PCA, although a formal classification framework has recently been developed in order to "improve the uniformity of definition of the syndrome" (Crutch et al., 2017, p.1). However, the fact that a bias is manifest towards diagnosing patients with PCA based on predominantly right-hemisphere symptoms and patterns of atrophy is concerning. This suggests not only that half of patients with PCA will go un- or mis-diagnosed, but also that research concerned with developing an accurate profile of the disease (which in turn will lead to the development of reliable clinical diagnostic criteria) will be inherently unrepresentative, revealing only a portion of the true picture.

8.0.3 Neural Correlates of Cognitive Impairments in PCA

An imaging study by Kas and colleagues used brain SPECT in order to study regions of hypoperfusion in 39 patients with PCA, correlated with neuropsychological test scores in order to present an indication of the neural basis of PCA-specific symptoms, with particular reference to those relating to visuospatial functions (Kas et al., 2011). Figure 8.5 presents a visual representation of these results. This investigation represents the only systematic investigation published to date into the neural correlates of symptoms specific to PCA.

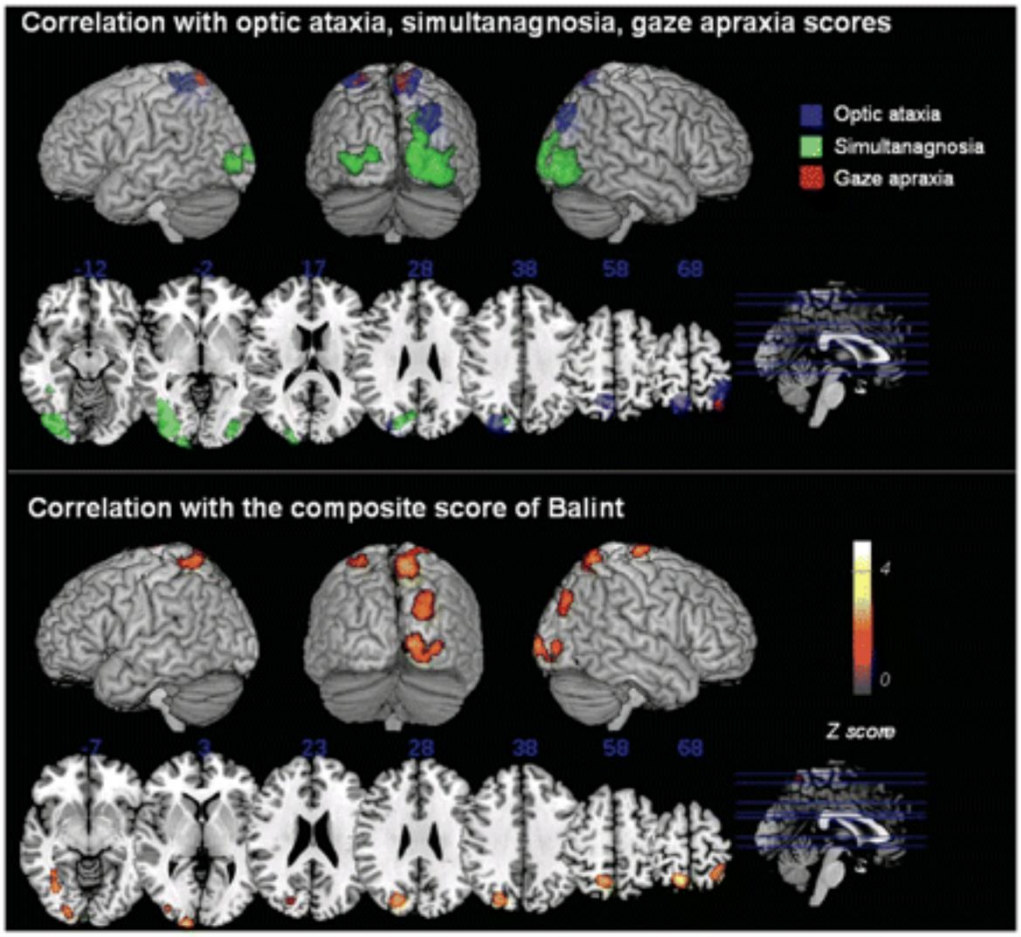


Figure 8.5: Neural Correlates of Simultanagnosia, Optic Ataxia, Gaze Apraxia and Bálint's Syndrome Scores
Top: Positive correlations between cerebral perfusion and optic ataxia (blue), simultanagnosia (green), and ocular apraxia (red) scores (all $P < 0.005$ uncorrected). Bottom: Positive correlation between the scores for Bálint's syndrome and cerebral perfusion. Transacial slices are shown according to radiological convention. (from Kas et al., 2011).

Bálint's syndrome (comprising optic ataxia (OA), simultanagnosia (SA), and ocular apraxia (OA)) was correlated to perfusion in the dorsal parietal and occipital lobes, precuneus and cuneus (with right predominance) (Kas et al., 2011). OA was found to be specifically correlated with hypoperfusion of the bilateral superior parietal cortex and right precuneus (Kas et al., 2011). SA was related to the lateral occipital cortex, extending to the right cuneus, precuneus and temporo-occipital junction (Kas et al., 2011). Gerstmann scores were found to be correlated significantly with parietal hypoperfusion in the left angular cortex, but no significant correlation was found for brain atrophy and finger agnosia, agraphia or verbal working memory (Kas et al., 2011).

8.0.4 Aims

The aim of this investigation was to assess correlations between Koedam scores and measures of visual-attentional and visuomotor performance of PCA and non-PCA patients, and to describe posterior atrophy in the current cohort of patients.

8.1 Method

8.1.1 Ethical Approval

See Chapter 4, Section 4.1.1 for details.

8.1.2 Recruitment

Clinical recruitment was conducted according to the outline provided in Chapter 4, Section 4.1.2. Brain images were assessed from all participants, where possible, who completed Phase 1 testing.

8.1.3 Participants

Brain imaging results were available and subsequently analysed from 23 of the 26 patients who completed Phase 1 testing. It was not possible to generate Koedam scores for two patients as a consequence of limitations in available scan images (for both patients only CT scans were available), and a further one patient was omitted due to a matching error of NHS CHI number.

Diagnostic Group No.	Diagnostic Group Description	Number of Patients in Group	Mean Age at Date of Consent to Phase 1 [range]	Gender	
				Female	Male
1	PCA	5	61.02 [51.34-69.59]	3	2
2	AD	7	64.72 [55.72-71.38]	3	4
3	FTD	8	65.69 [57.84-73.52]	3	5
4	Aphasia	3	68.78 [64.48-71.51]	2	1
5	LBD/CBD	2	70.42 [62.79-78.05]	1	1

Table 8.1: Demographic Characteristics of Patients in Brain Morphology Analysis

8.1.4 Procedure, Materials & Measures

Visual analysis of brain imaging scans was conducted with the aid of Professor Adam Waldman (AW), Chair of Neuroradiology at the Centre for Clinical Brain Sciences at the University of Edinburgh. Koedam scores were generated for all patients within the sample by AW, using the most recent brain imaging scans as the basis for the score for each participant.

There was variability in the quality and availability of different scan types for analysis, with volumetric scans being available for 40% of patients (n = 10).

8.2 Analysis

Initial visual analysis of brain scans was conducted by AW on January 15th, 2018. AW used the Koedam scale in order to assess for posterior cortical atrophy on each scan.

Table 8.2, below, presents details each individual patient included in the correlation analysis, with years from diagnosis to scan, years from scan to testing (the most recent scan available, used to generate that individual's Koedam score), and Koedam score.

Patient No.	Current Diagnosis	Years from diagnosis to scan	Years from scan to testing	Koedam Score
16	Aphasia	5	**-1	3
1	PCA	*-1	4	2
12	CBD	5	0	2
6	AD	0	1	2
4	PCA	0	2	1
7	FTD	*-1	4	1
9	FTD	0	1	1
10	FTD	0	1	1
25	FTD	0	2	1
26	DLB	0	1	1
8	Aphasia	0	1	1
14	AD	1	2	1
15	AD	0	3	1
20	AD	*-1	1	1
2	PCA	4	0	0
11	FTD	*-1	2	0
13	FTD	1	3	0
23	FTD	*-1	4	0
27	Aphasia	2	1	0
17	AD	1	1	0
18	AD	*-1	4	0
21	AD	0	1	0
24	AD	0	2	0

Table 8.2: Brain Morphology Time Scale Data
Note: * scan happened prior to diagnosis, ** testing happened prior to scan.

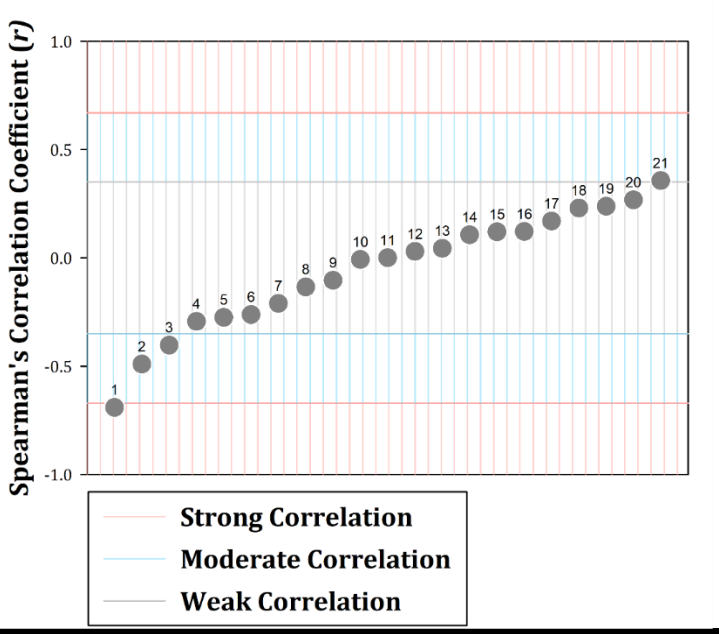
An initial data cleaning exercise was undertaken in which dependent variables with fewer than 10 observations were removed from further analysis. The grasping, matching, and pointing task were filtered out as a result.

Following this, an exploratory Spearman's correlation analysis was conducted between Koedam scores and the dependent variables (which were summary scores from the tasks and experiments conducted across Phase 1 and Phase 2 testing).

Given the high number of variables included in the Spearman's correlation analysis, the false discovery rate (FDR) adjustment was applied in order to limit the Type I error rate. This method is considered more powerful than the Bonferroni method (Benjamin & Hochberg, 1995).

8.3 Results

None of the correlations calculated reached statistical significance. However, given that these analyses are exploratory in nature, it is reasonable to assess the strength of the association between Koedam score and the dependent variables included in the analysis, rather than whether the association reached statistical significance (Field, 2013; Nakagawa & Cuthill, 2007).



DV No.	DV Descriptor	n	r	*p* (FDR Adjusted)
1	Obstacle Avoidance - Avoidance Bias (AvB)	11	-0.690	0.233
2	Posner - Cue Effect (CFX)	13	-0.490	0.492
3	Visual Search - Conjunction - Reaction Time (RT)	14	-0.403	0.518
4	Visual Search - Pop-out - Targets Absent Percentage Accuracy	15	-0.293	0.637
5	Bisection - Gap - Endpoint Weightings Bias (EWB)	18	-0.274	0.627
6	Visual Search - Pop-out - Percentage Accuracy	15	-0.261	0.687
7	Visual Search - Conjunction - Percentage Accuracy	15	-0.210	0.772
8	Obstacle Avoidance - Avoidance Sum (AvS)	11	-0.134	0.904
9	Visual Search - Conjunction - Target Absent Percentage Accuracy	13	-0.103	0.928
10	Cancellation - Visible - Total Time	23	-0.007	0.989

11	Cancellation - Invisible - Median *x* Co-ordinate	23	0.001	0.998
12	Cancellation - Visible - Median *x* Co-ordinate	23	0.030	0.982
13	Visual Search - Pop-out - Median No. Saccades	15	0.044	0.974
14	Visual Search - Conjunction - Median No. Saccades	13	0.107	0.925
15	Bisection - Gap - Directional Bisection Error (DBE)	21	0.120	0.819
16	Visual Search - Conjunction - Mean Saccadic Amplitude	13	0.122	0.904
17	Bisection - Line - Directional Bisection Error (DBE)	21	0.170	0.761
18	Bisection - Gap - Endpoint Weightings Sum (EWS)	18	0.230	0.687
19	Cancellation - Invisible - Total Time	23	0.238	0.627
20	Bisection - Line - Endpoint Weightings Bias (EWB)	19	0.268	0.627
21	Bisection - Line - Endpoint Weightings Sum (EWS)	19	0.357	0.516

Figure 8.6: Plot of Spearman Correlation Coefficient *r* Scores and Table of *r* and FDR-adjusted *p* Scores
Key: * = significant at α = 0.05. DV = dependent variable.

Figure 8.6, above, presents Spearman's correlation coefficients between Koedam scale score and all other dependent variables included in the analysis. For the purposes of this analysis, a weak correlation is defined as a coefficient ≤ 0.35, a moderate correlation is considered between 0.36 and 0.67, and a strong correlation is between 0.68 and 1 (Taylor, 1990).

Only four dependent measures correlated with Koedam score with a strength greater than weak. These were the obstacle avoidance measure of AvB (strongly negatively correlated), Posner CFX (moderately negatively correlated), the conjunction visual search task's measure of RT (moderately negatively correlated), and finally the line bisection measure of EWS (moderately positively correlated).

8.4 Discussion

Following adjustment for multiple comparisons, none of the correlation coefficients reached a satisfactory level of statistical significance. However, given the exploratory nature of these analysis, it can still be considered reasonable to assess the strength of the relationship, despite the lack of significance. Four of the dependent measures demonstrated correlation coefficients which could be considered moderate. These included the obstacle avoidance AvB measure (r = -0.690), the Posner CFX (r = -0.490), conjunction visual search RT (r = -0.403) and the line bisection measure of EWS (r = 0.357). Therefore, as Koedam score increased, there was an associated increase in asymmetry of avoidance observed in the obstacle avoidance task, a decrease in the cueing effect for the Posner task, and a decrease in RT on the conjunction visual search task – as well as an increase in EWS observed on the line bisection task.

The association between Koedam score and obstacle avoidance AvB and conjunction seems intuitive. Relating these results to results obtained in prior chapters, an increase in parietal atrophy is likely to be associated with abnormalities in obstacle avoidance, as automatic avoidance behaviour is a dorsal stream mediated function (Schindler et al., 2004) (see Chapter 6 for further details). The dorsal stream of visual processing, as proposed by Goodale and Milner, projects from the V1 through the posterior parietal cortex (Goodale & Milner, 1992). Impaired obstacle avoidance, as well as impairments in both pointing and grasping objects in the visual periphery are all considered symptoms of optic ataxia (a dorsal stream disorder), thus associated with damage to the posterior parietal area (Meek et al., 2013). Note that control participants tend to show a marginally greater influence of the ipsilateral object position on avoidance tasks, therefore observing an association with increasing posterior parietal atrophy and a greater weighting given to the contralateral object position is suggestive of possible optic ataxia-like deficits.

However, the relationships between Koedam score and Posner CFX as well as conjunction visual search RT and line bisection EWS are rather more complex to interpret. Simultanagnosia and visual neglect are disorders of visual attention associated with damage to the dorsal visual stream. Both of these disorders would be predicted to be associated with an increases in RT for conjunction visual search, rather than decreases (which the results of the present study imply) (see Chapter 5 for further details). Similarly, a high CFX score on the Posner task indicates a greater cost of invalidly over validly cued targets on response RT. This pattern is well-established, and can be reliably observed for control participants. Increasing levels of parietal atrophy would therefore most likely be associated with increases in CFX score, as patients with visual neglect (strongly associated with posterior parietal damage) may exhibit a disengage deficit – whereby shifting their attention from the invalidly cued non-neglected side to the true target location on the neglected side incurs a greater cost in RT, and thus an increase in CFX (rather than a decrease, which the present results suggest) (see Chapter 5 for further details). Finally, EWS on the line bisection task is a proposed measure of total attention, with 1 being the maximum attainable score representing total attention, and a score close to zero indicating a lack of attention. In other words, an insensitivity to the changing endpoint positions of the stimuli (see Chapter 5 for further elaboration). Posterior parietal damage is strongly associated with disorders of visual attention (such as visual neglect), and thus increases in Koedam score would theoretically be more likely to be associated with decreases in EWS, rather than increases which the present results suggest (see Chapter 5 for further details on visual neglect and EWS).

It therefore seems plausible that these 'inverted' relationships may be a consequence of performance on the task being dependent on additional cognitive processes, which may lie outside of the posterior parietal cortex region and thus be preserved in individuals within the present sample who have a high Koedam score. It is also possible that noise in the data, particularly in light of the small sample size and great degree of between-subject variability

both in terms of diagnosis as well as level of disease progression, may affect these results. Chapter 4 presents a case study of a PCA patient (patient 6), in whom control-level performance on many visuoattentional and visuomotor tasks was reported, despite their advanced state of parietal atrophy (Koedam score of 2). Thus, it seems a high Koedam score does not necessarily imply impaired abilities on tasks which challenge the posterior parietal cortex, and vice versa, a low Koedam score does not necessarily imply preserved abilities on these tasks.

These exploratory correlation analyses are limited by a number of factors. The first and perhaps most vital limitation to consider is that it was not possible to adjust the Koedam scores to account for time elapsed since scan. The scans used for generation of Koedam scores were performed, on average, 0.57 years (SD = 1.80) following diagnosis. Testing on the dependent measures included in this analysis occurred, on average, almost two years after the scan date (mean = 1.74 years, SD = 1.39). Thus, the Koedam scores used in the present analysis were likely an underestimation of the true Koedam score for that individual at the time of testing. Naturally, the rate of progression differs hugely between individuals and between dementia types. It is impossible to approximate or predict what the Koedam score would be on the date of testing for each individual without performing new scans. As such, it is therefore important to note that Koedam scores used in this task provide only an approximation of the true extent of posterior parietal atrophy for each patient at the time of testing. Similarly, there was a great degree of variability in terms of the quality of scans available for analysis in this study, with high resolution, volumetric scans available for just 40% of the present sample. This may introduce a systematic bias in terms of the accuracy of the Koedam score generated, with some being more accurate than others as a function of the availability of better resolution scans. The high degree of variability in scan quality and time between scan and testing introduce a considerable amount of error to these results. A further limitation to these analysis is the small sample size. In addition, visual rating scales are a rather coarse measure of atrophy – which thus introduces another

element of potential noise to these data. In other words, noisy brain measures (such as visual rating scales) may not be predictive of noisy behavioural measures.

9. Modelling Optic Ataxia

9.0 Introduction

9.0.1 Defining Optic Ataxia

Optic ataxia (OA) is a higher-order deficit of visually guided actions, and is typically defined by manual misreaching errors to visual targets (Andersen, Andersen, Hwang & Hauschild, 2014; Blangero et al., 2007; Buxbaum & Coslett, 1997; Striemer et al., 2009). Commonly, OA results from lesions to the dorsal posterior patietal cortex, specifically the superior parietal lobule (SPL) and areas around the intraparietal sulcus (IPS), and may affect one or both hemispheres (Karnath & Perenin, 2005; Blangero et al., 2007; Striemer et al., 2009; Andersen, Andersen, Hwang & Hauschild, 2014). OA can manifest as misreaching to targets in the contralesional visual field, difficulty preshaping the hand for grasping, and deficits in correcting reaches on-line following initiation of the movement (Andersen et al., 2014). Studies which map the specific reaching errors observed in OA patients consistently find that patients are relatively unimpaired near central, foveal vision, but that reaching errors dramatically increase with retinal eccentricity (Khan et al., 2005; McIntosh, Mulroue, Blangero, Pisella & Rossetti, 2011).

OA often occurs as one of a triad of symptoms along with simultanagnosia and ocular apraxia, together forming Bálint's syndrome (Andersen, Andersen, Hwang & Hauschild, 2014). The notion of "pure" OA was described by Perenin and Vighetto where OA was observed in isolation, without any other symptoms of Bálint's syndrome (Perenin & Vighetto, 1988; Striemer et al., 2009). One study which aimed to find a common lesion location across patients with 'pure' OA found a region of convergence involving the IPS and SPL, which falls within the area thought to subserve the dorsal stream of visual processing (Rossetti, Pisella & Vighetto, 2003; Goodale & Milner 1992; Milner & Goodale, 1995;

Milner & Goodale, 2008). The dual stream hypothesis of visual processing postulates that the ventral stream is concerned with perceptual visual processing (often referred to as the 'what' stream), whereas the dorsal stream is concerned with 'vision for action' (the 'where' or 'how' stream) (Goodale & Milner 1992; Milner & Goodale, 1995; Milner & Goodale, 2008). Thus, as a disorder of the dorsal stream, 'pure' OA has been considered a condition with no associated perceptual deficits (Pisella, Rossetti & Rode, 2017).

Traditionally, therefore, the diagnosis of OA required that perceptual deficits be excluded from any explanation of target misreaching. However, recent studies have empirically demonstrated that there is impaired discrimination of object location or orientation in extrafoveal vision (Pisella et al., 2009; Perenin & Vighetto, 1988; Michel & Henaff, 2004; Rossetti et al., 2005; Striemer et al., 2008). Such perceptual impairments have been postulated to reflect a reduced capacity to orient attention within or towards the ataxic field (McIntosh et al., 2011). Indeed, numerous studies have now demonstrated reduced orienting of attention in the ataxic field in OA patients as well as impaired online correction of movements, which may suggest that attention is indeed implicated in reaching errors for these patients (Striemer et al., 2009; McIntosh et al., 2011). Lesions to the posterior parietal region are not associated with primary sensory or motor deficits, thus OA reaching errors cannot be attributed to deficits in the visual or motor systems alone, but rather reflect deficits at an integrative, sensorimotor level (Andersen et al., 2014; Khan et al., 2005).

Pointing errors typical of OA are presented in Figure 9.1, below, from OA patients AT and IG (Rossetti et al., 2005; Milner, Dijkerman, McIntosh, Rossetti & Pisella, 2003). Pointing errors are generally hypometric and medial (undershooting the target and towards fixation) for patients with OA, and this pattern can readily be observed both for immediate and delayed pointing in both patients (Figure 9.1). There is also a tendency for pointing errors to be hypermetric at the nearest eccentricities for OA patients, and this can be seen particularly clearly in both error plots from patient AT (Figure 9.1, plot A) and

particularly in the delayed pointing condition for patient IG (Figure 9.1, plot B). It is conceivable that these hypermetric errors at nearest eccentricities and hypometric errors further from fixation are the consequence of abnormalities in cortical magnification (further elaboration on this is presented in Chapter 5).

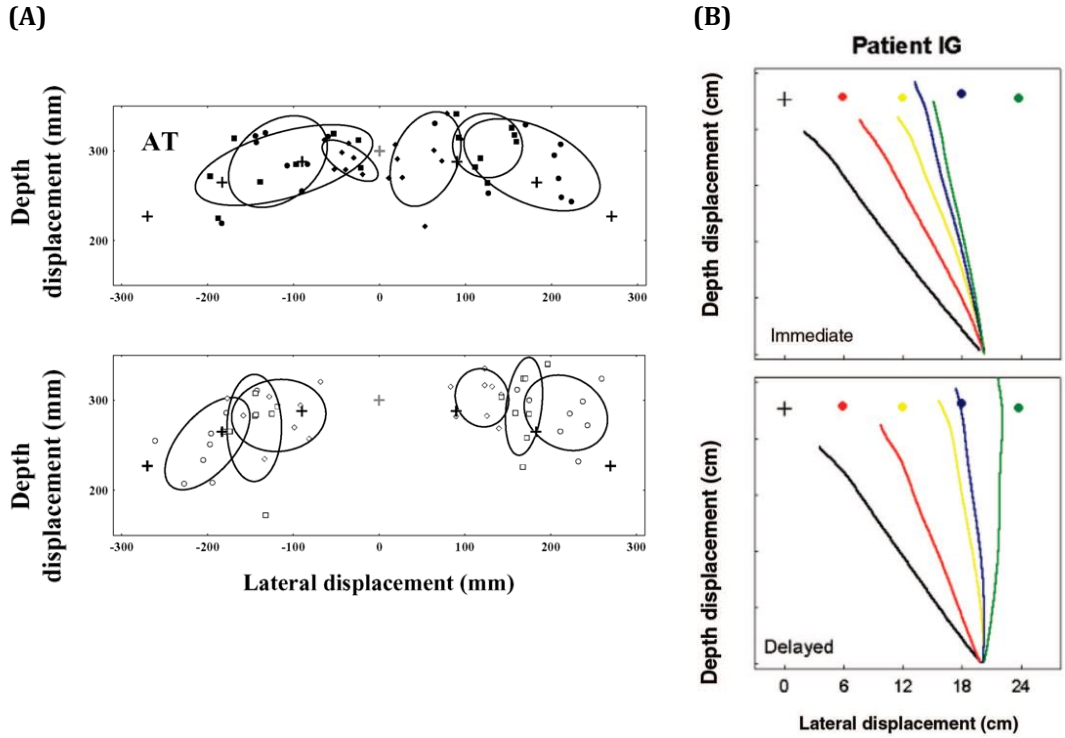


Figure 9.1: OA Pointing Errors from Patient AT (A) and IG(B)
(A) Spatial plot of pointing performance for patient AT in immediate (upper row) and delayed (lower row) conditions. Confidence ellipses (95%) were fitted to the pointing scatter for each target (from Rossetti et al., 2005).
(B) Immediate and delayed pointing trajectories in patient IG averaged over the depth points common to all reaches. Hypometric (e.g. leftward) errors are evident for patient IG in both conditions (from Milner, Dijkerman, McIntosh, Rossetti & Pisella, 2003).

Many studies cite a 'paradoxical improvement' of reaching errors in OA when a delay between target presentation and pointing movement is introduced (Milner, Dijkerman, McIntosh, Rossetti & Pisella, 2003; Milner, Paulignan, Dijkerman, Michel & Jeannerod, 1999; Revol et al., 2003). The explanation offered for this apparent improvement is that introducing a delay leads reaches to be guided more by the ventral (perceptual) rather than dorsal stream of visual processing (Milner et al., 1999). It seems more accurate to describe the errors as weaker, rather than improved, following delayed reaching. OA

pointing errors form a distinctive, reproducible pattern under both immediate and delayed conditions with the magnitude of errors lessened under delayed conditions. Figure 9.2, below, presents typical OA and control pointing behaviour in immediate and delayed pointing conditions, illustrated by absolute pointing error values (Milner, Paulignan, Dijkerman, Michel & Jeannerod, 1999).

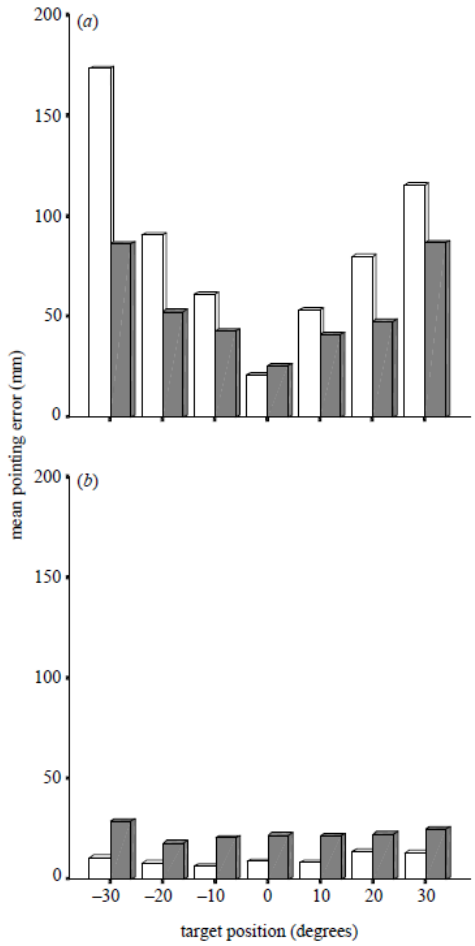


Figure 9.2: OA Absolute Pointing Errors from Patient AT and Control CM in Immediate and Delayed Pointing
(a) Mean pointing errors made by Patient A T. to a target L.E.D. immediately after its onset (unfilled bars) or following a delay of 5 seconds (filled bars).
(b) Mean pointing errors made by control subject C. M. following immediate pointing (unfilled bars) or following a delay of 5 seconds (filled bars).

Interestingly: performance for control participants can worsen under delayed pointing conditions (see Figure 9.3, below, for further examples from control CM) (Rossetti et al., 2005).

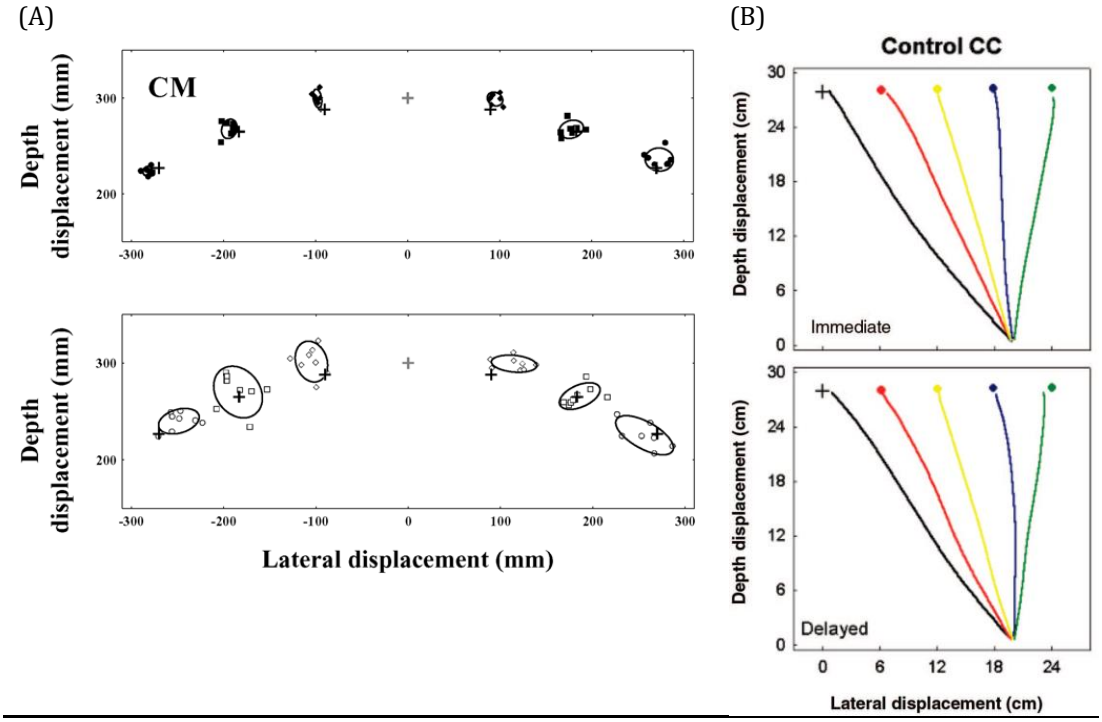


Figure 9.3: OA Pointing Errors from Control CM: Greater Errors Under Delayed Pointing
(A) Spatial plot of pointing performance for control CM in immediate (upper row) and delayed (lower row) conditions. Confidence ellipses (95%) were fitted to the pointing scatter for each target (from Rossetti et al., 2005).
(B) Immediate and delayed pointing trajectories in control CM averaged over the depth points
common to all reaches (from Milner, Dijkerman, McIntosh, Rossetti & Pisella, 2003).

The apparent 'improvement' seen in OA patients under delayed pointing conditions may provide a clue as to the neural processes which underlie the misreaching errors observed in these patients generally. The PPC is considered a multisensory, integrative centre, receiving input from both visual (occipital cortex) and proprioceptive (anterior parietal cortex) senses (Blangero et al., 2007). The highly reproducible pattern of errors under immediate and delayed pointing suggest that each condition requires a different set of computational processes to complete. Theories which attempt to explain these patterns typically refer to the delayed condition as requiring more ventral (perceptual visual short-term memory) processing (Milner, Dijkerman, McIntosh, Rossetti & Pisella, 2003). Some authors have suggested that dorsal and ventral visual streams are concerned with egocentric (body-centered) and allocentric (object-

centered) representations, respectively (Chen, Byrne & Crawford, 2011). Thus, introducing a delay in pointing forces subjects to rely more on less accurate allocentric representations (Chen et al., 2011). Therefore for OA patients it is possible that the less dramatic errors observed in delayed pointing are due to the reliance on allocentric processing, whereas immediate pointing relies perhaps solely on an egocentric frame of reference. Of course, allocentric representations must be converted to egocentric commands in order for the reach to be initiated (Chen et al., 2011). The errors observed for delayed pointing may therefore occur as a consequence of this transformation via a 'faulty' dorsal visual stream.

9.0.2 Attention and Action as Interdependent Systems

Whether attention is implicated in visually-guided action performance remains a hotly contested debate within the literature. Aligning with the traditional, dissociative dual stream hypothesis, Liu and colleagues claim that identification of one object interferes with the *planning* of a pointing action towards a second object, but does not interfere with the visually guided control required to complete the action (Liu, Chua & Enns, 2008). Thus, the dorsally-mediated control of action is seen as a 'zombie' mechanism once initiated - automatic and unconscious (Liu et al., 2008; Ro, 2008). However, a number of studies have presented results which contradict this assertion, whereby perceptual attention to a stimulus other than the 'action' target disrupts the individual's ability to make online corrections or scale their grip appropriately, thus suggesting interference effects from perception on action performance, which implies a common attentional resource (Similä & McIntosh, 2015; Hesse & Deubel, 2011). Furthermore, 'action' behaviour has been found to be modulated by attentional load which further supports the hypothesis of a shared mechanism in visuomotor performance (Blangero et al., 2010; Rossetti et al., 2005).

There have been a number of models proposed which attempt to account for how attentional selection (or allocation of attention) relates to selection-for-perception (SfP) and selection-for-action (SfA) (Similä & McIntosh, 2015). Milner and Goodale originally addressed this distinction by suggesting that SfA determines the allocation of perceptual attention, but SfP does not reciprocally constrain action guidance (Similä & McIntosh, 2015; Milner & Goodale, 1995). Other theories have proposed more closely associated links between SfA and SfA (Similä & McIntosh, 2015). The influential but controversial premotor theory of attention (a reworking of the Oculo Motor Readiness Hypothesis by Klein (1980)) asserts that in order to attend visually to an object, a plan for a visually-guided action towards that object must be created, regardless of whether that action is subsequently taken (Rizzolatti, Riggio, Dascola & Umiltá, 1987; Smith & Schenk, 2012). This assertion is based, in part, on the hypothesis posed by this theory that the neural substrates for spatial attention are the same as those involved in the planning and execution of actions (Smith & Schenk, 2012). Thus, according to the premotor theory, SfA and SfA should always co-occur because they are equivalent (Rizzolatti, Riggio, Dascola & Umiltá, 1987; Smith & Schenk, 2012; Similä & McIntosh, 2015).

In contrast, the Visual Attention Model (VAM) proposes that vision for perception and action share an early selection mechanism, whereby the early visual representation of an object leads to the formation of an 'object token' via chunking of this early representation (Schneider, 1995). This model assumes that visual attention serves two main functions, selection-for-object-recognition and selection-for-space-based-motor-action (Schneider, 1995). Thus, perceptual features of the object token are forwarded to the ventral stream for object recognition, and location and spatial features are prioritized for motor action and sent to the dorsal stream (Schneider, 1995). Therefore, in the VAM the distinction between SfP and SfA relates to the behavioural motive as to why the object was selected - the target becomes prioritized for both perception and action simultaneously (Schneider, 1995; Similä & McIntosh, 2015).

Relating the hypothesis posed previously i.e. that immediate and delayed pointing requires egocentric and allocentric visual processing, respectively, to the models of visual attention described above, it is conceivable that the initial process of attentional selection is degraded for patients with OA. Thus, both SfP and SfA are operating at a deficit. However, SfP and hence allocentric visual processing is advantaged (perhaps prioritized from a limited attentional resource), thus therefore reaches following a delay, which require more perceptual processing are observed to be less degraded than immediate (egocentric, dorsally mediated) reaches.

For this reason, Both the VAM and the premotor theory of attention predict that SfP and SfA co-occur simultaneously, which stands in contrast to the original assertion by Milner and Goodale that action guidance can be independent of perceptual attention (Similä & McIntosh, 2015; Schneider, 1995; Rizzolatti, Riggio, Dascola & Umiltá, 1987; Milner & Goodale, 1995). The consensus within the literature is that attention is a limited-capacity resource, and allocation of attention (and processing of irrelevant stimuli) is determined by the attentional demands of given task (Lavie, 2005; Kastner & Ungerleider, 2000; Schwartz et al., 2005). Misreaching errors observed in OA may therefore be a consequence of a deficit in attentional capacity; with a reduced attentional resource, the available attention is likely to be exhausted by perceptual demands more quickly and thus lead to deficits in visually-guided action (e.g. misreaching errors), given that SfP and SfA appear to share the same limited resource. It is also possible that the deficit observed in OA is due to a deficit in attentional allocation (discussed further in Section 9.3.2 of the present chapter).

9.0.3 Aims

The aim of this experiment was to test the hypothesis that visuomotor performance on a pointing task will be modulated by a concurrent attention

task at fixation, in order to ascertain whether perception and action performance rely on a common attentional resource.

9.1 Method

9.1.1 Ethical Approval

This study received full approval from The University of Edinburgh's Psychology Research Ethics Committee, reference number: 206-1415/3.

9.1.2 Recruitment

Participants were recruited using the online recruitment portal 'mycareerhub', hosted by the University of Edinburgh (mycareerhub.ed.ac.uk). The advert called for any adult over the age of 18 with no known neurological or visual deficits. Participants were offered £5 per hour to take part, with an anticipated total test duration of one hour.

9.1.3 Participants

This study was piloted on three healthy volunteers in order to ensure that the computer code for each condition operated correctly and in order to establish a good estimate for the duration of each condition of the experiment, and therefore the experiment as a whole. This in turn was used to inform participants the anticipated duration of the experiment, and to estimate the cost of running the experiment.

Eighteen healthy adults (15 female, 3 male) were subsequently recruited. Participants had a mean age of 29 years (SD = 13.45).

9.1.4 Procedure, Materials & Measures

This experiment utilised a dual-task paradigm, in which a visuomotor reaching task was performed concurrently with a visual attention task at fixation.

Participants placed their head on a chin rest mounted to the table in order to maintain a viewing distance of 570mm from the point of fixation. A demonstration program was run before commencing the experiment, which gave participants the chance to familiarize themselves with the dual task requirements, and to practice responding to the touch stimuli and fixation stimuli in tandem. Following the demonstration, instruction sheets were provided before each block to ensure that participants were fully informed of targets at fixation to which they were required to respond.

The task had three conditions, corresponding to different degrees of attentional load. The attentional load was manipulated by altering the fixation target criterion. The order of presentation of these conditions was counterbalanced across participants. Each participant completed six blocks, two per load condition. The pointing task parameters were the same across each condition, with 'touch' targets presented in a random order. The task program was custom written in PsychoPy.

The visuomotor component of the task involved participants reaching out with the index finger of their right hand from a marked starting position (50mm in front of them) to touch white, circular targets. The touch targets would 'flash' on-screen for a total duration of 500ms, and participants were instructed to try and touch the targets before they disappeared, whilst maintaining fixation at the centre of the screen. This was intended to promote rapid responses. The delay between the touch response and the next target appearance was 2000ms. Targets were 30 pixels in diameter.

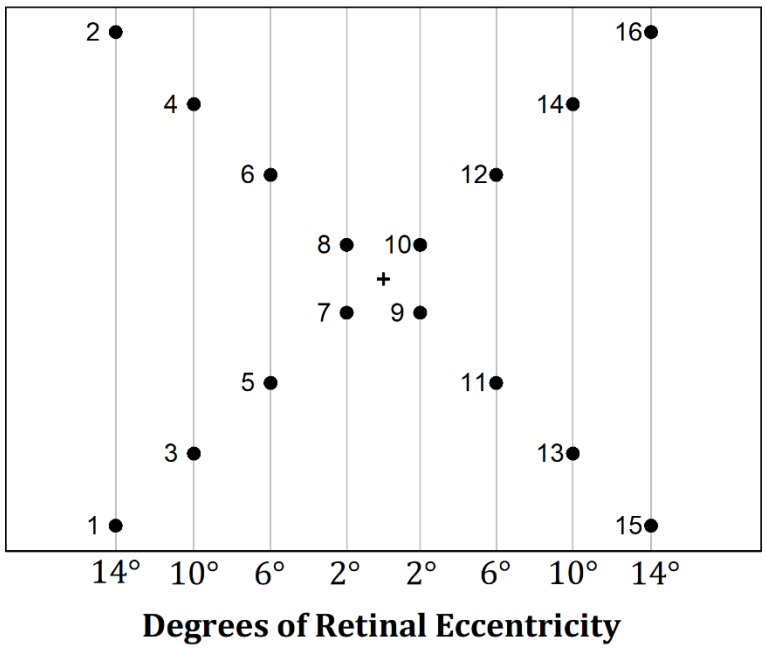


Figure 9.4: Modelling Optic Ataxia: Target Locations
• Represents target location with target number code.

The touch targets appeared at any one of 16 target locations, presented across four radial arms at different degrees of retinal eccentricity (2°, 6°, 10°, 14°) (see Figure 9.4, above). Each target appeared 5 times per block, therefore 10 times per condition. Targets appeared on-screen sequentially, in random order.

Participants were required to maintain fixation on the screen centre throughout each block in order to complete the concurrent attentional load task. Participants were required to monitor a constant stream of upright or inverted crosses, presented in the centre of the screen (crosses were 30 pixels in height). The task instructions were to press a button on a wireless keyboard using their left hand whenever a target cross appeared. A new cross appeared every 500ms, with a delay of 500ms between each. The three attentional load conditions and the specified target for each are detailed in Figure 9.5, below.

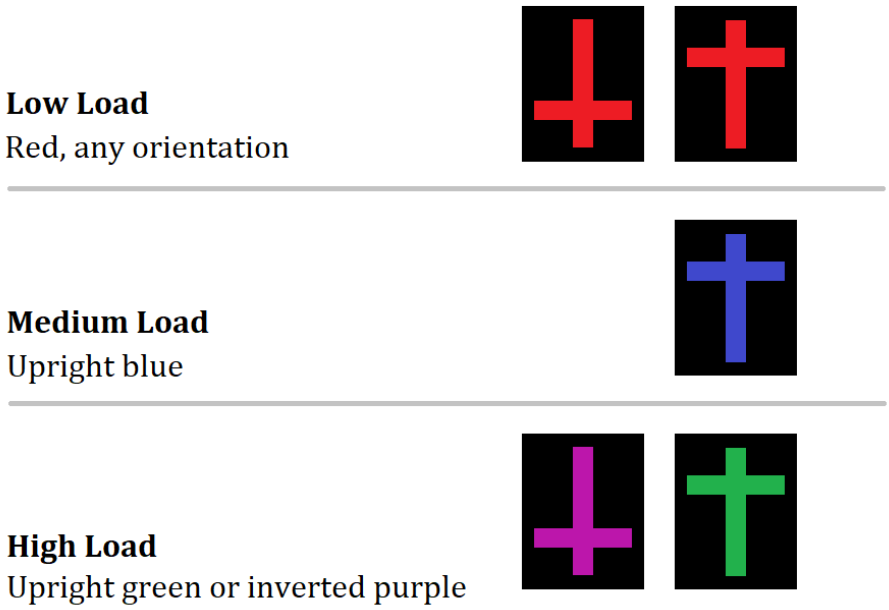


Figure 9.5: Target Criterion for each Attentional Load Condition

The load of the task was therefore manipulated by varying the complexity of the target criterion, but the probability of a target within the stream was always 7.5%. The design of the load task was based on previous research reported by Lavie (2005).

Figure 9.6, below, presents a representation of a trial.

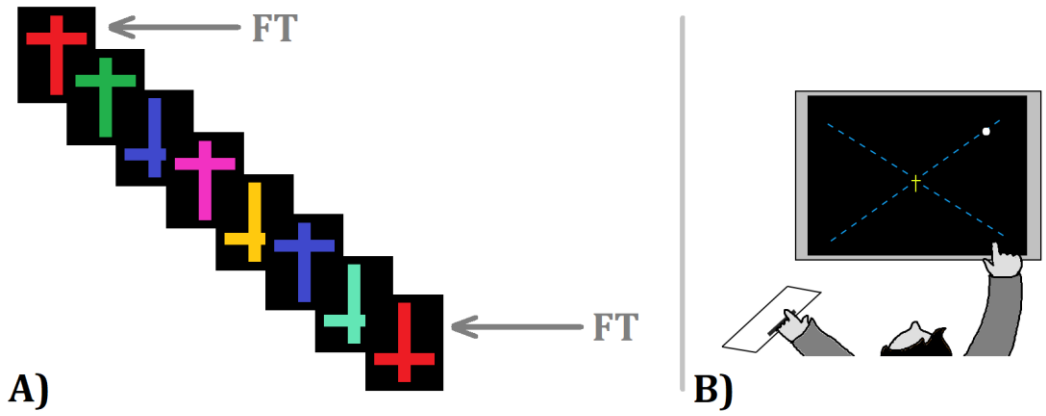


Figure 9.6: A) Example Stream of Fixation Stimuli and B) Experimental Set Up
Note: FT = fixation target. A) This example presents the low attentional load task, where a red cross in any orientation was the fixation target. The participant pressed a key on the keyboard with their left hand (B), maintaining fixation on the stream of crosses, while concurrently reaching with their right hand to respond to the touch stimuli.

9.1.5 Analysis

For the purpose of analysis, errors were recoded such that those towards fixation (hypometric) were negative, and errors away from fixation (hypermetric) were positive. Data were screened prior to analysis as a data cleaning exercise, in which the following rules were applied:

Dependent Variable	Exclusion Rule	Justification	No. of cases excluded (% of total trials)
Reaction time (RT)	RT <400ms, exclude the trial as anticipatory	Visual inspection of the histograms revealed a local minimum of 400ms, therefore RTs of <400ms were coded as anticipatory.	15 (0.17%)
RT	RT >3000ms, exclude the trial as missed touch target	RTs greater than 3000ms were coded as missed targets, as reaches after 3000ms were likely to be memory-guided, rather than online.	47 (0.54%)

Table 9.1: Modelling Optic Ataxia: Data Cleaning Exclusion Criteria

Amplitude error was calculated using the following formula:

$$Response\ amplitude = \sqrt{((response\ x)^2 + (response\ y)^2)}$$

$$Target\ amplitude = \sqrt{((target\ x)^2 + (target\ y)^2)}$$

$$Amplitude\ error = response\ amplitude - target\ amplitude$$

This dependent variable was calculated in order to measure both the magnitude of the error as well as the distance from fixation.

In addition, amplitude shift was calculated in order to illustrate the difference in amplitude error of the medium and high load conditions compared with the low load condition. This was calculated using the following formula for a given target eccentricity:

$$Amplitude\ shift = high\ /\ medium\ load\ amplitude\ error - low\ load\ amplitude\ error$$

9.2 Results

Figure 9.7 presents the mean amplitude error values for each attentional load condition. This plot clearly illustrates hypermetria at the nearest eccentricity, and pronounced hypometria at the further eccentricities, particularly for the medium and high attentional load conditions: reminiscent of OA-like errors.

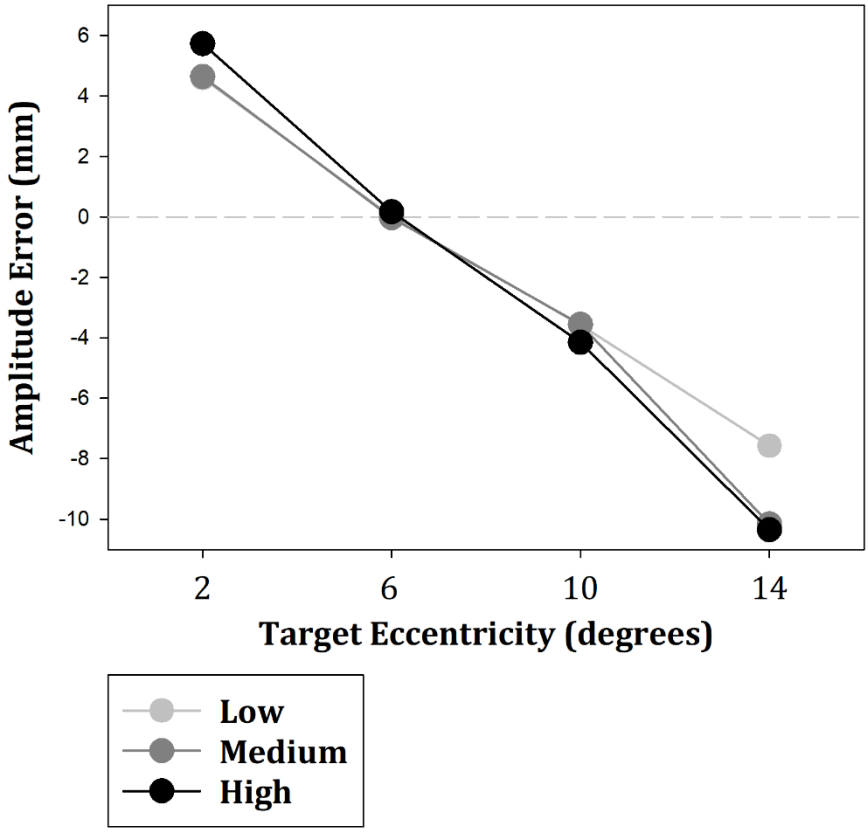


Figure 9.7: Amplitude Error
Note: - - - represents no error (zero line).

In order to formally assess differences between conditions and target eccentricities, a repeated measures ANOVA was conducted. The results indicated a significant main effect of target eccentricity, $F(3, 15) = 14.417$, $p = 0.000$, a significant main effect of side, $F(1, 17) = 5.226$, $p = 0.035$, as well as significant side by eccentricity interaction, $F(3, 15) = 6.682$, $p = 0.004$, and significant load by eccentricity interaction, $F(6, 12) = 3.178$, $p = 0.042$.

Analysis of the simple, simple main effects indicated a significant difference between the left and right side at the furthest eccentricity (14° retinal eccentricity), $p = 0.005$, but no significant differences in mean amplitude error between the left and right side at 2° ($p = 0.626$), 6° ($p = 0.640$), or 10° ($p = 0.111$) of retinal eccentricity.

Analysis of the simple, simple main effects of eccentricity by attentional load condition revealed differences between the low and high attentional load conditions at the nearest eccentricity (2°), $p = 0.017$, and furthest eccentricity (14°), $p = 0.012$. Significant differences between the low and medium attentional load conditions emerged only at the furthest target eccentricity, $p = 0.027$. The medium and high attentional load conditions did not differ significantly across target eccentricities. These results are further represented in Figure 9.8 (amplitude shift).

The significant simple, simple main effect of side at the furthest target locations is likely driven by the fact that participants responded to touch targets with their right hand only, therefore reaching across their midline to the furthest targets on the left hand side may have caused greater amplitude errors than reaches to the furthest eccentricity targets on the ipsilateral side.

The results indicated a significant interaction between attentional load condition and target eccentricity, with greater magnitude errors at the furthest target eccentricities for all attentional load conditions. Errors appeared hypermetric at the nearest eccentricity, and consistently and increasingly hypometric at further target eccentricities.

In order to illustrate this pattern, amplitude shift was calculated and is plotted on Figure 9.8, below.

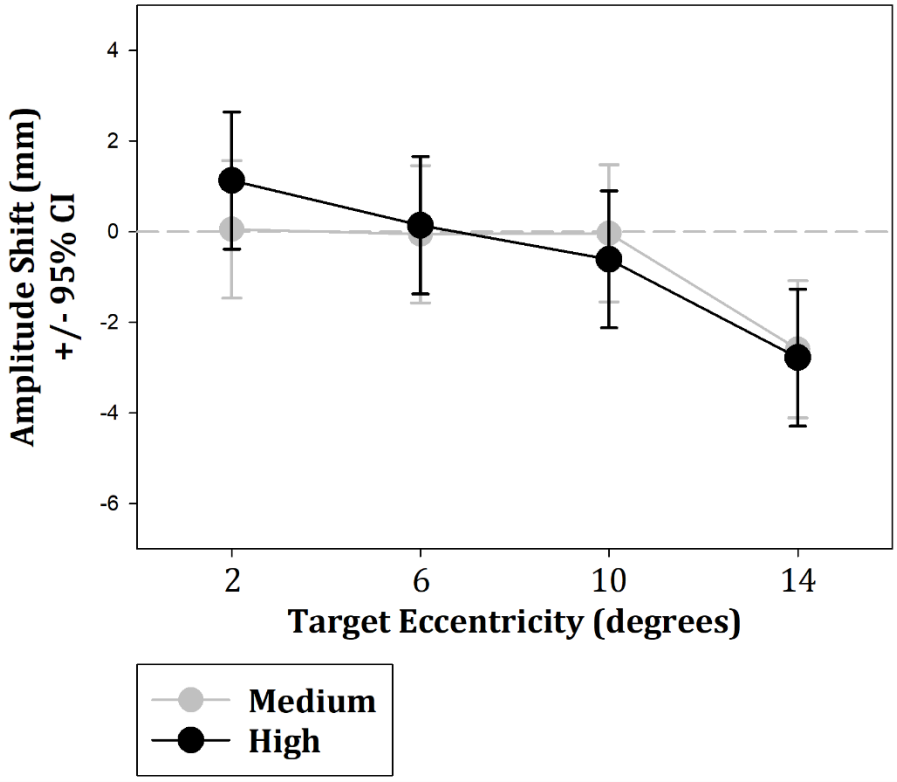


Figure 9.8: Amplitude Shift (with between-subject confidence intervals).
Note: - - - represents origin line.

Figure 9.8 illustrates the difference in mean amplitude between the low load condition and the medium and high load conditions. From this plot it is clear that the high load condition results in a greater magnification of the amplitude error patterns, with a greater degree of hypermetria at the nearest eccentricity, and marginally (but not significantly) greater hypometria at the furthest eccentricities compared to the medium load condition.

9.3 Discussion

The results mimic the misreaching errors commonly observed in OA patients with a bias towards fixation and increasing in magnitide with increasing eccentricity, observed in immediate (as well as delayed) reaching conditions (Chang & Abrams, 2004; Hesse & Deubel, 2011; Schwartz et al., 2005; Revol et

al., 2003). A similar pattern of errors was observed in healthy controls in this experiment using an attentional load manipulation. Pointing errors in this experiment were observed to 'overshoot' the touch target at locations close to fixation (hypermetria), and to 'undershoot' the touch target at locations peripheral from fixation (hypometria).

These results suggest that attention load modulates visuomotor performance in healthy controls. Extrapolating from these results, it may be that attentional load and deficits thereof are therefore implicated in the impaired performance seen in OA patients. These implications are discussed below.

9.3.1 Attentional Load as a Modulator of Visuomotor Performance

The present experiment is novel in the application of a pointing task with concurrent attentional load task. Prior research investigating the effect of attention on visuomotor control has typically been concerned with the effect of attention on grasping performance (Baldauf & Deubel, 2010; Hesse & Deubel, 2011; Hesse, Schenk & Deubel, 2012). The results of the present study lend support to the hypothesis that attention is implicated in visually-guided action. The results demonstrated a significant load by target eccentricity interaction, with greater amplitude errors with increasing attentional load and increasing target eccentricity. Thus, attentional load was observed to modulate visuomotor performance. These findings additionally support the view of attention as a limited-capacity resource, from which SfP and SfA are drawn. If SfP exceeds a certain threshold, then deficits in visuomotor behaviour are observed, as the distribution of attention is weighted towards perception to the detriment of action. In other words, if attention is required at the point of fixation, then there are insufficient resources to encode the location of peripheral targets, leading to reaching errors.

What makes the results of the present study so relevant to understanding attention and action is that they indicate that visually-guided actions are not simply an automatic, 'zombie', dorsal-stream mechanism, but require attentional resources and thus are impacted when available attention becomes limited. This finding is supported by prior literature on grasping which has demonstrated that effective control of grasp kinematics (that is, appropriately scaling the hand prior to the grasp) requires attentional resources - with less accurate planning and control of grasp movements occurring in the context of a concurrent perceptual task (Hesse & Deubel, 2011; Hesse, Schenk & Deubel, 2012).

9.3.2 Attentional Load and Optic Ataxia

The results of the present study may offer some insight into the cognitive processes which drive the characteristic pointing errors observed from patients with OA, and thus serve as a potential model for OA in the healthy brain.

One of the fundamental lines of evidence in support of the dual-stream view of visual processing was that of a double-dissociation observed between OA and visual agnosia (VA) (Cardoso-Leite & Gorea, 2010). OA, resulting from lesions to posterior parietal areas, was considered a disorder of the dorsal visual stream, whereby patients with 'pure' OA would have intact visual discrimination abilities (Cardoso-Leite & Gorea, 2010; Pisella, Rossetti & Rode, 2017). In contrast, patients with damage to ventral-stream areas experience visual agnosia (VA) – an inability to recognise or identify objects, thus a disorder of visual perception (Cardoso-Leite & Gorea, 2010; Pisella, Binkofski, Lasek, Toni & Rossetti, 2006). The assertion of a double-dissociation between OA and VA is increasingly flimsy, with evidence demonstrating deficits in perception for OA patients within their ataxic visual field, as well as recent evidence of OA in patient DF (a widely-studied visual form agnosic) (Striemer et al., 2007; Rossit

et al., 2018). These streams of evidence challenge the notion of a double dissociation between OA and VA, as they provide evidence that the two streams of visual processing may not be functionally entirely separate, as they were originally conceived as being by Milner and Goodale (Goodale & Milner 1992; Milner & Goodale, 1995; Milner & Goodale, 2008).

Converging lines of evidence from neuropsychology as well as dual-task studies in healthy participants therefore suggest that ventral and dorsal stream functions are not cleanly dissociated, but rather appear to interact during performance of visuomotor tasks (Himmelbach & Karnath, 2005). Results from the present study suggest that deficits observed in OA may be a consequence of a reduced attentional capacity, thus the attentional resource quickly becomes depleted by perceptual demands, leading to errors in visuomotor behaviour.

Perhaps, similarly to the model of mutual hemispheric inhibition in visual attention proposed by Kinsbourne (1970), the dorsal and ventral streams may mutually inhibit the attentional resource consumption of the other stream in the healthy brain. Thus, following lesions to dorsal-stream mediated areas, the balance of attentional resource consumption may shift, such that priority is given to ventral stream processes, leading to deficits in visually-guided motor behaviours due to a limited 'portion' of attention being provided to these functions. An 'inhibition of attentional allocation' (IAA) model is therefore proposed. This IAA model is based on the principles of the VAM, whereby an early attention selection mechanism allocates information for ventral or dorsal stream processing (Schneider, 1995).

The proposed model represents total attentional capacity as a limited resource, within which a flexible boundary exists, and which allocates portions of attention to ventral or dorsal stream processing, contingent on task demands. This flexible boundary is mediated by a mutual inhibition of the alternative stream, such that the dorsal stream inhibits attentional allocation to the ventral stream and vice versa. This mutual inhibition therefore allows allocation to be

determined by the task demands, for example: a dorsally-demanding task will lead to greater inhibition of the ventral stream allocation. The model proposes that in a neurologically normal brain under a perceptually-demanding dual-task condition (such as that described within the present investigation), the allocation boundary shifts, allocating a greater portion of the total available attentional resource to the ventral stream, thus leading to errors in the dorsally-mediated pointing task as a result of reduced attention available for dorsal stream processing. This model proposes, therefore, that OA patients (following dorsal stream lesions) have a pathologically biased allocation of visual attention, such that the ventral stream of processing receives a greater allocation as a consequence of the absent, or reduced, inhibition of ventral stream allocation as a consequence of the PPC lesions. These patients therefore exhibit deficits in visuomotor performance when attention cannot be deliberately allocated to the dorsal-stream functions – by means of foveating the target. Therefore, extrafoveal targets must rely on a small allocation of total attention, leading to characteristic visuomotor errors.

An fMRI study, which investigated the neural basis of attentional load using a visual motion-tracking paradigm, found evidence to suggest a general role for the PPC in the deployment of attentional resources (Jovicich et al., 2001). Perhaps, therefore, the PPC could be the locus of the inhibitory mechanisms proposed within this model. Although the IAA model may serve to explain the characteristic deficits in visuomotor performance observed for OA patients, it does not explain the nature of the pointing errors, particularly the pattern of hypermetria for targets close to fixation and hypometria for more eccentric targets.

However, the IAA model does not sufficiently explain why OA patients have been observed to demonstrate deficits in perception in extrafoveal vision (Pisella et al., 2009; Perenin & Vighetto, 1988; Michel & Henaff, 2004; Rossetti et al., 2005; Striemer et al., 2008), nor why OA-like pointing errors have been observed in VA patient DF (Rossit et al., 2018; Hesse, Ball & Schenk, 2012,

2014). An alternative and simple explanation is that OA does not represent a perception/action dissociation, but rather the central versus peripheral distinction for visuomotor performance (Schenk, 2006; Rossetti, Pisella & Vighetto, 2003; Clavagnier, Prado, Kennedy & Perenin, 2007). This theory suggests that OA patients will therefore be impaired for peripheral, but not central, tasks (Rossetti, Pisella & Vighetto, 2003). Patient DF has, until recently, been a central element in support of the perception and action dissociation. Crucially, DF's apparently preserved VM performance was always observed in central vision. It is only recently that authors have tested her performance in peripheral vision, and have found evidence of OA (Rossit et al., 2018; Hesse, Ball & Schenk, 2012, 2014).

9.3.3 Suggestions for Future Research

The results of the present study offer an interesting insight into the possible mechanisms behind OA pointing errors, serving as a model for this behaviour within the healthy brain. Replication studies would be a valuable first step for future researchers in order to establish the reliability of these results. Similarly, future studies may benefit by introducing a more attentionally demanding task at fixation, such as an N-back task. Additionally, it would be valuable to determine the effect of limited visual feedback on pointing errors for healthy individuals. This could be achieved by using a semi-silvered mirror, for example, to prevent visual feedback of the hands during pointing movements. It is likely that this would result in pointing errors of a greater magnitude. Participants in the present study responded to touch targets with their right hand only, and used their left hand to respond to the attention task. It would be valuable to establish whether there are differences in the magnitude of pointing errors between the left and right hand, thus establishing whether a 'hand effect' could be modelled within healthy participants, as is often observed in OA patients (McIntosh, Mulroue, Blangero, Pisella & Rossetti, 2011).

10. General Discussion

The primary aim of this thesis was to characterise the visuomotor and visuoattentional abilities of patients with PCA, as well as those of patients with other, related, neurodegenerative diseases. Through the testing process it became apparent that PCA patients were often extremely impaired, sometimes appearing functionally blind, and occasionally demonstrating results which were rendered uninterpretable as a result of their profound visual deficits. For example, some PCA patients were so visually impaired that they could not locate the computer screen which was directly in front of them. As a consequence, the data gathered from the assessment of PCA patients was rather heterogeneous, and often complex to interpret, although some interesting results pertaining to the screening of PCA patients have emerged from this thesis which may in turn inform future research in this field, and perhaps even influence clinical practice.

The most striking and potentially important results from this thesis were not related to PCA at all – but pertain to typical AD. Thus, results from the secondary aim of this thesis, which was to characterise the visuoattentional and visuomotor deficits in patients with diagnoses other than PCA, were the most prominent.

This thesis also served to provide supplementary support for recent studies which have found evidence of optic ataxia (OA) in patient DF, leading to questions over the dogma which placed DF – a visual form agnosic – in a keystone position in support of the dual stream theory of visual processing (Goodale & Milner 1992; Milner & Goodale, 1995; Milner & Goodale, 2008).

10.0 Future Directions for Screening for PCA

One of the central aims of the screening phase of assessments was to establish the sensitivity and specificity of a battery of different assessments in discriminating PCA patients from those with other neurodegenerative diseases

(NDDs). The most sensitive and specific task was found to be the Modified Luria Alternating Square and Triangles (M-LAST), closely followed by the cancellation task and the bisection task.

The M-LAST task is a simple and quick pencil-and-paper task in which the subject is asked to copy a line of alternating, connected geometric shapes. This task has not, at the time of writing, been used in the assessment of PCA patients. Following further research, this test could have considerable potential for use diagnostically. In addition, the test is appealing as it can be used to identify two symptoms, both visuo-constructional apraxia (VCA) and closing-in behaviour (CIB). VCA, or constructional dyspraxia, was identified by Crutch and colleagues as diagnostic of PCA in the recently published formal classification framework for the disease, and was reported as the fourth most prominent symptom of PCA (Crutch et al., 2017). In the patient sample studied herein, VCA was not observed for any patient other than those with PCA, and thus yielded an impressive 100% specificity. CIB, observed strikingly for a number of the PCA patients, is often noted in patients with VCA but may be an independent process (Conson, Salzano, Manzo, Grossi & Trojano, 2009). CIB was observed in a number of diagnostic groups screened, and thus was not specific to PCA like VCA was, however the sensitivity was found to be 100%.

Using control-generated cut-offs for normality, the line bisection and cancellation tasks were both found to be particularly sensitive and specific to PCA. Notably, it was the alternative form of the traditional bisection task, gap bisection, which yielded the greatest sensitivity across the two alternative forms for PCA (which has not, at the time of writing, been used in any other study of PCA patients). Similarly, the results were variable for the two alternative conditions of the cancellation task (visible and invisible) which were presented to patients. During the screening phase, it was the visible cancellation task which appeared most specific to PCA (92.86% for visible, 42.86% for invisible), with the alternative 'invisible' cancellation condition being more sensitive (100% sensitivity for invisible, 60% for visible). However, more

elaborative analysis of the cancellation tasks identified two alternative dependent measures which provided far greater sensitivity and specificity to PCA than the standard measure of target omissions, particularly when using cut-offs for normality generated from patient rather than control data (reported in Chapter 5). It was found that the measure of 'total time' could yield a specificity of 92.86% for PCA across both the visible and invisible cancellation conditions – with sensitivity of 80% and 100%, respectively. These impressive values were a consequence of the interesting finding that PCA patients, almost without exception, continued to search the visual array for targets in the invisible condition until the test timed-out. Similarly, the dependent measure of 'median *x* co-ordinate' was highly specific to PCA (100% for both conditions), and appeared more sensitive in the invisible (80%) than the visible (60%) condition. This increased sensitivity in the invisible condition may be a consequence of this condition revealing more neglect when compared with the visible condition, an explanation posited by previous authors (Wojciulik, Rorden, Clarke, Husain & Driver, 2004).

During the screening phase it was the alternative form of the bisection task (gap bisection) which appeared more revealing of deficits specific to PCA patients, with a sensitivity of 75% (compared to just 40% for the more traditional line bisection task). As with the cancellation task, further analysis was conducted using alternative dependent measures which echoed these results, finding the gap bisection condition generally more sensitive and specific to PCA (see Chapter 5). The traditional dependent measure of directional bisection error yielded superior sensitivity and specificity values when contrasted with alternative measures (endpoint weighted bias and endpoint weighted sum). Arguably, none of the measures captured the most striking behaviour, which was observed in two of the PCA patients, where optic ataxia (OA) in one patient and extreme simultanagnosia in the other caused them to respond by only touching the endpoints of the stimuli in the gap condition. Thus, bisection as a screening tool may have a great deal of potential in discriminating different visuoattentional symptoms, particularly those associated with presentations of

PCA, but alternative metrics are required to maximise the diagnostic potential of this test.

The sensitivity and specificity values attained from these three tests can be contrasted with those associated with, for example, the Elementary Visual Features domain total score (see Chapter 4 for further details) – the constituent BORB subtests of which are related to the tasks included in the ACE-III visuospatial domain, which demonstrated a less impressive specificity of 68.75% for PCA. It should be noted, however, that these results are preliminary patterns based on a very small sample of PCA patients, but nonetheless offer an interesting alternative to more traditional methods of assessing visuoattentional deficits associated with PCA in the clinic.

10.1 Optic Ataxia as New Biomarker for AD

The results of a potentially groundbreaking recent study have thrown into focus the possible value of using the detection of symptoms of OA for early diagnosis of AD. This longitudinal study on autosomal dominant AD investigated the pathophysiological cascades which lead to AD, and identified the precuneus as the region in which each of the waves of change first occur (the waves being Aβ plaque formation, tauopathy, altered glucose metabolism, and finally structural decline) (Gordon et al., 2018). Changes in the precuneus region may be present for up to 20 years prior to the onset of typical symptoms of AD, such as memory problems (Gordon et al., 2018). The precuneus has been associated with episodic memory retrieval, but is more strongly associated with the visual guidance of reaching (Gordon et al., 2018; Cavanna & Trimble, 2006; Karnath & Perenin, 2005). Thus, it is feasible that sensitive and specific tasks, specifically developed in order to detect OA-like symptoms (such as misreaching to peripheral targets), may represent the next evolution of screening tests which could be used to detect changes, possibly even in the preclinical phase of the disease. Development of such tests could thus aid disease diagnosis and prognosis (Pike et al., 2007).

Perhaps the most prominent, novel, and potentially groundbreaking finding to emerge from this thesis was that of strong evidence of OA in patients with AD. Three of the four AD patients who completed the pointing task exhibited hypometric errors, increasing in magnitude with increasing target eccentricity (see Chapter 6 for further details), reminiscent of the results obtained by DF on the same task. Presentations of OA are strongly associated with damage to the precuneus, an area identified as crucial for dorsal stream visual processing, and appearing particularly critical for the control of visually-guided action (Cavanna & Trimble, 2006; Karnath & Perenin, 2005). Taken in context with the recently published longitudinal imaging results from Gordon and colleagues, who have identified the precuneus as the first brain region in which each of the pathological cascades associated with AD start (Gordon et al., 2018), the present results appear to indicate that OA could well be an indicator of a neurodegenerative disease process for those patients in whom there is no evidence of stroke. Screening for OA could become a vital tool in the early detection of AD - potentially sensitive to AD-associated changes in an individual decades earlier than other neuropsychological screening measures, such as memory tests.

No prior study has identified symptoms of OA in patients with typical AD, perhaps in part because where OA is identified, the dementia is assumed to be atypical. However, there have been a number of studies which have identified the potential utility of visuospatial tests for both the diagnosis of dementia and the differentiation of AD from non-AD dementias (Salimi et al., 2018; Harciarek & Jodzio, 2005; Iachini, Iavarone, Senese, Ruotolo & Ruggiero, 2009; Tiraboschi, Salmon, Hansen, Hofstetter, Thal & Corey-Bloom, 2006). There are clues within the literature indicating that dorsal stream dysfunction (specifically, visuomotor deficits) may be more common in typical AD than previously thought. For example, there is a body of evidence which indicates deficits in both visual processing speed and visual short-term memory in both MCI and AD patients

(Bublak, Redel & Finke, 2006; Habekost & Starrfelt, 2009; Bublak et al., 2011; Janoutová, Šerý, Hosák & Janout, 2015). It has been proposed that simultanagnosia (SA) manifests as a consequence of impairments in visual information processing speed (Bundesen, 1990; Neitzel et al., 2017; Chechlacz et al., 2012), and also as a consequence of reductions in visual short-term memory capacity (Neitzel et al., 2017; Chechlacz et al., 2012). It seems plausible, therefore, that SA may be more common in AD than is currently thought, considering how commonplace deficits in visual processing speed and short-term memory capacity appear to be for AD patients. SA is one of a triad of related symptoms forming Bálint's syndrome, which is associated with bilateral parietal damage (Andersen, Andersen, Hwang & Hauschild, 2014). Other symptoms associated with Bálint's syndrome are ocular apraxia and, crucially, OA (Andersen et al., 2014). As well as being a possible causal mechanism leading to SA, slowed visual processing could be interpreted as an inability to use visual information for immediate action, which is the defining quality of OA.

Close examination of the literature provides further evidence demonstrating dorsal stream dysfunction in AD patients, with authors suggesting that dorsal visual stream functions may be more impaired in AD than ventral stream functions (Prvulovic et al., 2002). More common are studies which identify dorsal visual stream regions as characteristic regions of early atrophy in AD. One study, for example, noted cortical thinning in the precuneus - often at the earliest stages of the disease - which has led to atrophy in this region being interpreted as one of a number of 'cortical signatures' of AD along with additional brain regions (such as medial temporal, inferior temporal, inferior parietal and temporal pole areas) (Dickerson et al., 2009; Karas et al., 2007). Interestingly, one study, which identified the precuneus specifically as a region of atrophy in early-onset AD, noted the common association between lesions to the precuneus and OA in stroke patients (Karas et al., 2007).

Diagnosis of AD typically occurs once, or shortly after, the emergence of dementia (Gordon et al., 2018; Bastin & Salmon, 2014). However, as the paper by Gordon and colleagues illustrates, the pathobiology of AD precedes dementia by decades (Gordon et al., 2018; Frisoni, Fox, Jack Jr., Scheltens & Thompson, 2010; Braak & Braak, 1991; Aisen, 2009). The pre-dementia period is considered the best target for therapeutic interventions (Bastin & Salmon, 2014; Reiman et al., 2011; Karran, Mercken & De Stooper, 2011). A study by Brookmeyer and colleagues projected that a treatment which could delay the onset of AD symptoms by only 5 years (without increasing life expectancy), could reduce the number of clinically affected individuals by half – thus, therapeutic interventions targeted at the earliest stage of AD could have enormous public health implications (Brookmeyer, Gray & Kawas, 1998; Reiman et al., 2011). This illustrates the value of early diagnosis of AD in order to provide targeted interventions at the earliest possible stage.

It is possible that the lack of documented evidence for OA in typical AD patients is the consequence of both of an absence of research along with a failure to 'connect the dots' from other neuropsychological studies, which have reliably identified damage to the precuneus with presentations of OA (Jackson et al., 2009; Karnath & Perenin, 2005; Himmelbach et al., 2009). The value of investigating the presence of OA in AD patients has flown under the radar until now. Historical and contemporary evidence, together with that gained from testing patients within the present study, indicates the importance of the precuneus within the AD disease process. Thus, it may be that screening for OA will become a vital future tool for the detection of AD in its earliest stages.

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12. Appendices

12.1 Appendix 1: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	11
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	11-53
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	11-15
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	15
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	16
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	17
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	17
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	17
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	18
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any	N/A

		assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	20
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	23

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	23
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	24
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	20
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	43
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	50-51
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	N/A
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	52-53
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

12.2 Appendix 2: Data Extraction Form

Adapted from information taken from: Wright, R. W., Brand, R. A., Dunn, W. & Spindler, K. P. (2007). How to Write a Systematic Review. *Clinical Orthopaedics and Related Research, 455;* 23-29.

CITATION	
SYSTEMATIC REVIEW INDEX NUMBER	
TITLE	
AUTHORS	
YEAR	
JOURNAL INFORMATION	

INTRODUCTION	
RESEARCH QUESTION	
SECONDARY RESEARCH QUESTIONS	
SECONDARY RESEARCH QUESTIONS	
HYPOTHESIS (1)	
HYPOTHESIS (2)	
HYPOTHESIS (3)	

METHODS	
STUDY TYPE	CORRELATIONAL | DESCRIPTIVE | EXPERIMENTAL
TIME SCALE	RETROSPECTIVE | PROSPECTIVE | CROSS-SECTIONAL | LONGITUDINAL
RESEARCH DESIGN	ARCHIVAL | CASE STUDY | EXPERIMENT | INTERVIEW | OBVSERVATIONAL | QUASI-EXPERIMENTAL | SELF-REPORT | SURVEY
OTHER INFO	
STUDY DESIGN	
APPOPRIATE STUDY DESIGN USED?	
INDEPENDENT VARIABLE(S)	
DEPENDENT VARIABLE(S)	
TEST OF ATTENTION USED?	
TESTS OF ATTENTION	
TEST OF VM ABILITIES USED?	
TESTS OF VM ABILITIES	
CONTROL GROUP	
OTHER FACTORS NOT CONTROLLED FOR	
PROSPECTIVE OR RETROSPECTIVE	
POTENTIAL SOURCES OF BIAS	
INDEPENDENT EXAMINERS USED TO DETERMINE OBJECTIVE OUTCOME DATA?	
VALIDATED OUTCOME MEASURE USED	
OUTCOME MEASURES	
SPECIFIC PCA SYMPTOMS BEING INVESTIGATED	
PRESENTING PCS SYMPTOMS DESCRIBED	
INCLUSION/EXCLUSION CRITERIA	

2 | Data Extraction Form.

POPULATION INFORMATION	
DEMOGRAPHIC INFO – COUNTRY	
DEMOGRAPHIC INFO – GENDER	
DEMOGRAPHIC INFO – AGE	
PCA PATIENTS	
PCA DIAGNOSTIC CRITERIA	
OTHER PATIENTS	
OTHER DIAGNOSTIC CRITERIA	
PATIENTS AT FOLLOW-UP: PCA	
OTHER PATIENTS AT FOLLOW-UP	
POPULATIONS HAVE SIMILAR CHARACTERISTICS?	
LENGTH OF FOLLOW-UP	
DIFFERENCES IN POST-TREATMENT CARE OR ASSESSMENT	

STATISTICAL APPROACH	
STATISTICAL TESTS USED	
EFFECT SIZES – COHEN'S d	
EFFECT SIZES – ODDS RATIO	
EFFECT SIZES – HAZARD RATIO	

RESULTS	
RESULT 1 – DESCRIPTION	
RESULT 1 – POINT ESTIMATE	
RESULT 1 – P VALUE	
RESULT 1 – STATISTICAL SIGNIFICANCE	
RESULT 2 – DESCRIPTION	
RESULT 2 – POINT ESTIMATE	
RESULT 2 – P VALUE	
RESULT 2 – STATISTICAL SIGNIFICANCE	
RESULT 3 – DESCRIPTION	
RESULT 3 – POINT ESTIMATE	
RESULT 3 – P VALUE	
RESULT 3 – STATISTICAL SIGNIFICANCE	
RESULT 4 – DESCRIPTION	
RESULT 4 – POINT ESTIMATE	
RESULT 4 – P VALUE	
RESULT 4 – STATISTICAL SIGNIFICANCE	

Adapted from information taken from: Wright, R. W., Brand, R. A., Dunn, W. & Spindler, K. P. (2007). How to Write a Systematic Review. *Clinical Orthopaedics and Related Research, 455;* 23-29.

RESULT 5 – DESCRIPTION	
RESULT 5 – POINT ESTIMATE	
RESULT 5 – P VALUE	
RESULT 5 – STATISTICAL SIGNIFICANCE	
RESULT 6 – DESCRIPTION	
RESULT 6 – POINT ESTIMATE	
RESULT 6 – P VALUE	
RESULT 6 – STATISTICAL SIGNIFICANCE	

OTHER NOTES

12.3 Appendix 3: Reported Neuropsychological Assessments in PCA-Specific Papers

Assessment Category	Test Name	Frequency
14. General Dementia Screen		
	Clinical Dementia Rating Scale	4
	Blessed Dementia Rating Scale	2
	Cambridge Behavioural Inventory - Revised	2
	Cambridge Cognitive Examination	2
	Frontal Assessment Battery	2
	Proverb Interpretation Test	1
	Weigl's Sorting Test	1
	Cambridge Examination for Mental Disorders of the Elderly (CAMDEX)	1
15. Psychiatric & Quality of Life		
	Behavioural Assessment of the Dysexecutive Syndrome (BADS)	2
	Geriatric Depression Scale (GDS)	1
	Hospital Anxiety and Depression Scale (HADS)	1
	Activities of Daily Living (ADL)	1
	The Barthel Index	1
	The Rankin Grades	1
16. General Cognitive Abilities		
	Mini Mental State Examination (MMSE)	21
	Kolkata Cognitive Battery	18
	Wechsler Adult Intelligence Scale (WAIS)	5
	Seoul Neuropsychological Screen Battery (SNSB)	4
	The Cognitive Estimation Test (CET)	4
	The Warrington Concrete and Abstract Word Synonym Test – Semantic Knowledge Subtest	3
	Wechsler Adult Intelligence Scale – 3rd Edition (WAIS-III)	3
	WAIS-III – Visual Subtest	2
	Wechsler Adult Intelligence Scale – Revised (WAIS-R) – Performance Subtest	2
	Digit Copying Test	1
	Montreal Cognitive Assessment (MOCA)	1
	Montreal Cognitive Assessment (Japanese version) (MOCA-J)	1
	Wide Range Achievement Test – 4th Edition	1
	Mental Status Battery	1
17. Memory		
	Ray Auditory Verbal Learning Test (RAVLT)	2
	Visual Association Test (VAT)	2
	Wechsler Memory Scale (WMS)	2
	Wechsler Memory Scale - Revised (VMS-R)	2
	Consortium to Establish a Registry for Alzheimer's Disease - Clinical/Neuropsychological Battery (CERAD) – Verbal Learning Subtest	1

	CERAD – Free Recall Subtest	1
	CERAD – Recognition Subtest	1
	CERAD – Figural Recall Subtest	1
	CERAD – Savings Score Memory Subtest	1
	Free and Cued Selective Reminding Test	1
	Hopkins Verbal Learning Test (HVLT)	1
	Rivermead Behavioural Memory Test (RMBT)	1
	RBMT – Faces Subtest	1
	Wechsler Memory Scale - 3rd Edition (VMW-III)	1
	VMW-III – Visual Reproduction Recall Subtest	1
	VMW-III – Spatial Span	1
	VMW-III – Digit Span	1
	WAIS-R – Digit Span Subtest	1
	Benton Visual Retention Test	1
	Corsi's Block Span Test	1
18. Executive Functions		
	Clock Drawing Test – Copying (CLOX-2)	5
	Clock Drawing Test – Free Drawn (CLOX-1)	4
	Trail Making Test (TMT) - A	4
	CERAD – Verbal Fluency Subtest	4
	Controlled Oral Word Association Test (COWAT)	3
	Isaacs Set Test	2
	TMT - B	2
	Wisconsin Card Sorting Test (WCST)	1
	Raven's Coloured Progressive Matrices	1
19. General Early Visual Functions		
	The Visual Object and Space Perception Battery (VOSP)	4
	BORB – Length Match Subtest	2
	BORB – Size Match Subtest	2
	Cortical Vision Screening Test (CORVIST)	2
	CORVIST – Hue Discrimination Subtest	2
	CORVIST – Visual Acuity Subtest	2
	VOSP – Position Discrimination Subtest	2
	Efron Squares	2
	Poppelreuter-Ghent Overlapping Figures	2
	Bender Gestalt Test	1
	Benton's Judgment of Line Orientation Test	1
	Birmingham Object Recognition Battery (BORB)	1
	BORB – Orientation Match Subtest	1
	BORB – Position of Gap Match Subtest	1
	VOSP – Incomplete Letters Subtest	1
	Benton Visual Form Discrimination Test (VFD)	1
	VFD – Line Orientation Subtest	1
	Ishihara Colour Vision Test	1
20. General Late Visual Functions		
	Rey-Osterriech Complex Figure Test (ROCF)	4
	Hooper Visual Organisation Test (VOT)	3
	VOSP – Number Location Subtest	3
	The Visual Object and Space Perception Battery (VOSP) – Object Decision Subtest	2
	Modified Rey-Osterrieth Complex Figure Test	1

	VOSP – Unusual and Usual Views Subtest	1
	Complex Pictures Test (CPT)	1
	Test of Face Recognition	1
	Recognition of Famous Faces	1
	Street's Completion Test	1
21. Visual Attention & Neglect		
	Line Bisection	4
	VOSP – Shape Detection Subtest	2
	Benton Right-Left Orientation Test	2
	Bells Cancellation Test	1
	Mesulam Symbol Cancellation Task	1
	Neglect Examination Battery	1
	Luria Examination – Modified Alternating Square and Triangles Subtest	1
	VOSP – Incomplete Letters Subtest	1
	Behavioural Inattention Test	1
	Attentive Matrices	1
22. Visual Agnosia		
	Boston Naming Test (BNT)	7
	Boston Naming Test - Short Form Subtest	4
	Finger Agnosia Test	2
	Benton Visual Form Discrimination (VFD) – Finger Localization Subtest	1
	Object, Face and Colour Agnosia Screen (OFCAS)	1
	Visual Perception Test for Agnosia (VPTA)	1
	VOSP – Silhouettes Subtest	1
	Gollin Figure Test	1
	Pyramid and Palm Trees Test (PPT)	1
23. Simultanagnosia		
	VOSP – Dot counting Subtest	3
	Navon Figure Test – Global Shape Recognition	3
	Southern California Figure-Ground Visual Perception Test	2
	VOSP – Figure Ground Discrimination Subtest	2
	Boston Cookie Theft Picture	1
	Navon Figure Test – Local Shape Recognition	1
	BORB – Figure-Ground Segmentation Subtest	1
24. Speech & Language		
	Token Test – Short Form	3
	Western Aphasia Battery (WAB)	2
	WAIS-III – Vocabulary Subtest	2
	Lexicon and Morphology Test (LeMo)	1
	Oral Spelling Tests A & B	1
	Psycholinguistic Assessments of Language Processing in Aphasia (PALPA)	1
	WAIS-R – Verbal Subtest	1
	CORVIST – Reading Subtest	1
	Boston Diagnostic Aphasia Examination	1
	Short Story	1
	Word Fluency Test	1
25. Numeracy		
	Graded Difficulty Arithmetic Task (GDA)	2
26. Apraxia		
	Imitating Gestures	1

Table 12.3.1: Qualitative Assessment of Validated Neuropsychological Assessments in PCA Papers: All Reported Validated Assessments

Note: Many of these tests could be assigned multiple categories, therefore for simplicity tests have been organized into categories which they are most commonly associated with.

12.4 Appendix 4: Study Protocol V. 1.7

THE UNIVERSITY of EDINBURGH

Anne Rowling
Regenerative Neurology Clinic

Project Protocol

Visuospatial Perception and Motor Control in Posterior Cortical Atrophy (PCA), Corticobasal Degeneration (CBD) and related Neurodegenerative Diseases

Short Title

"Understanding Vision and Movement Changes in Neurodegenerative Disease"

Name of Applicants

Chief Investigator:
Miss Harriet Ingle**, PhD Student at the University of Edinburgh

Project Supervisors:
Dr. Rob McIntosh** (Primary Supervisor), Head of Psychology at the University of Edinburgh
Dr. Thomas Bak** (1st Secondary Supervisor), Lecturer at the University of Edinburgh
Dr. Suvankar Pal (2nd Secondary Supervisor), Consultant Neurologist at The Anne Rowling Regenerative Neurology Clinic.

KEY:
** denotes protocol authors.

List of Abbreviations

WHO - World Health Organisation
AD - Alzheimer's Disease
PCA - Posterior Cortical Atrophy
CBD - Corticobasal Degeneration
PPA - Primary Progressive Aphasia
BORB - Birmingham Object Recognition Battery
SMI - SensoMotoric Instruments
ANOVA - Analysis of Variance

Introduction

The World Health Organisation (WHO) identified dementia as a public health issue and a priority area for research in 2012 [1]. The number of people globally living with dementia during 2011 was estimated to be 35.6 million. Epidemiological studies suggest that this number will double by 2013, and triple by 2050 [1]. Dementia is the leading cause of dependency and disability across the world [1, 2], and is considered to be "The Silent Epidemic" [3] (p.2275), due to it's increasingly high prevalence rates and associated human and fiscal cost. Alzheimer's Disease (AD) is the most common type of dementia and usually presents in later life as problems with memory as well as impairments in other areas such as language, the ability to plan and problem-solve, and decreased or poor judgement [4, 5]. AD is increasingly becoming a more common cause of death across the world. In the United States of America during 2010, 32% of all older adult deaths (65 years or older) were attributed to AD [6]. By 2050 the proportion of deaths in this age bracket due to AD pathology is projected to be 43% [6]. In the United Kingdom an eight-fold increase in recorded AD deaths was observed for males, with a twelve-fold increase seen in females, between 1985 and 2004 [7]. AD is a very heterogeneous disease, with various subtypes already identified showing differences in age of onset, rate of decline, and profile of cognitive symptoms [4]. Classifying the different mechanisms of disease presentation and progression of these AD subtypes will allow for targeted rehabilitation as well as the development of sensitive and specific screening tools to aid in quicker diagnosis. Interventions for AD are most effective at the early stages of the disease, therefore rapid diagnosis is essential [8].

One subtype of AD is Posterior Cortical Atrophy (PCA). One of the defining features of PCA is a younger age of onset than typical AD. PCA is a rare, progressive dementia and is associated with a number of other neurodegenerative pathologies such as Creutzfeldt-Jacob Disease, AD, and Lewy body dementia [9-11]. PCA patients often display fewer memory deficits, better verbal fluency, and greater insight into their diagnosis than those diagnosed with typical AD [10]. Everyday symptoms which PCA patients may have include difficulties in reading, writing, and using familiar objects, as well as trouble interpreting road signs, and getting lost on familiar routes [11]. These symptoms can often be misinterpreted as having their origins in the eyes, rather than the brain [11].
The unique symptom profile of PCA and the unusually young age of onset mean that this subtype can often go undiagnosed for years at a time. There is some evidence suggesting that the clinical profile of typical AD and PCA may overlap in the latter stages of PCA disease progression [12], therefore PCA and AD may be part of the same disease process – or they may be clinically distinct syndromes.

The visual and co-ordination problems associated with PCA can be tested using a range of simple attention and movement tasks [12-14]. However, very few quantitative studies have been conducted with PCA patients. Further research to more fully understand the deficits observed in PCA patients would be a valuable step towards more effective diagnosis and better-targeted therapeutic strategies for this relatively newly-recognized form of dementia. Detailed research into AD subtypes, including PCA, will also shed light on the question of whether AD is a spectrum of disease, with different subtypes appearing somewhere across a shared scale, or whether these subtypes are actually clinically different from each other. This would allow for sensitive and specific screening tools to be developed to identify the unique symptoms of these subtypes of AD early, and prevent misdiagnosis and therefore delays in treatment. These specific problems with vision and movement may exist on a greater scale in other related diseases, such as in typical AD. Therefore a formal investigation into the prevalence and severity of these symptoms across a range of related diagnoses will grant an insight into an as-yet understudied area.

Global recognition of the scale of this growing ‘dementia epidemic’ have led to a more focused direction of research and resources into identifying dementia disorders at the earliest possible stage [3]. Diagnosing patients promptly and accurately can ensure that therapeutic interventions are provided early, sometimes slowing the progression of the disease. Expeditious diagnosis can improve the quality of life a patient with AD and their caregivers have as it allows for adequate institutional and home-based healthcare provisions to be planned for, as well as appropriate pastoral and ultimately palliative care to be sought [15]. Early diagnosis also allows

patients to plan and make decisions about their future health-care needs while they maintain the capacity to do so [16].

The aims of this project are; to investigate the visual, movement, and attention deficits which are characteristic of PCA and other subtypes of AD such as Corticobasal Degeneration (CBD), Primary Progressive Aphasia (PPA), as well as typical AD using a range of visual, attention, and movement tests, both in the clinic and in the lab. This will help to identify whether PCA and other subtypes of AD represent part of a common spectrum of impairment with typical AD, or whether they are distinct syndromes. This will allow the development of a sensitive and specific screening tool to be used in clinics to detect the earliest stages of symptom development for these rare diagnoses.

Hypotheses

1. Participants with PCA will demonstrate specific deficits on a battery of clinical tests assessing vision, hand-eye-coordination and language compared with other participant groups (AD, CBD, PPA). Participants with PCA will demonstrate greater deficits in tasks assessing visually-guided action and visuospatial attention compared with other domains (memory and language), than other participant groups (AD, CBD, PPA).

2. Amongst participants with PCA impairments of visually-guided action and controlled visual attention will be tightly linked, showing a similar within-participant profile. These attentional and visuomotor impairments will co-evolve and be strongly related over time.
3. An attentionally demanding task will exacerbate the specific visuomotor symptoms observed in PCA participants, allowing for the development of a sensitive and specific screening task to be developed.

Method

1. Participants

8 PCA participants have already been identified as interested in participating in research. In addition; participants with a diagnosis of CBD, PPA, or typical AD will be invited.

8 participants from each diagnostic group are anticipated to be recruited, with a total number of 32 research participants. A thorough review of related literature suggests that participant groups of this size are typical.

Inclusion criteria:

- Diagnosis of PCA, CBD, PPA, or AD
- Age over 18
- Anticipated survival of at least 12 months

Exclusion criteria:

- Inability to understand the consent process
- Enrolment in any other ongoing research project
- Patients who are in the terminal stages of the disease
- Participants with severe diabetes, epilepsy, alcohol/substance-related disorders, severe head injury (that required intensive care setting hospitalization), traumatic brain injury (inclusive of subarachnoid haemorrhage) and any other significant medical illness (such as stroke)
- Non English speakers

2. Design

a. General Overview

This study employs a mixed design. Within-subjects factors investigated are deficits on a range of visuospatial, attentional, and motor tests (in a clinical and lab-based setting) across time. The clinical setting is The Anne Rowling Regenerative Neurology Clinic, and the lab-based setting is the Visuomotor Laboratory at the University of Edinburgh. Both locations are fully accessible. Comparisons will also be made across the clinical and lab-based phases of the studies between-subjects; on relative impairment between participants of differing diagnoses for each assessment.

The outcome measures are therefore detailed case descriptions of participants with PCA and a comparison between PCA participants and participants with CBD, PPA, and AD on the extent to which specific visuomotor deficits are exhibited.

In-depth descriptions of the different phases of the study, and the assessments to be included within each, are presented below.

b. Project Procedure and Project Phases

Phase 1: Clinical Screening

Participants with typical and atypical presentations of AD and other neurodegenerative disorders (see above for a detailed list) will be recruited from the specialist outpatient clinic at the Royal Infirmary Hospital in Edinburgh; the Anne Rowling Regenerative Neurology Clinic.

Participants will be screened initially using a battery of assessments (see Table 1), targeting possible deficits usually associated with damage to the higher visual areas of the brain (ventral and dorsal streams). These assessments should therefore highlight any specific visual recognition, visual attention, and visuomotor deficits which participants may have. Testing will be conducted using paper-and-pencil tests and touch-screen tablets, and participants will have the opportunity to choose where to be assessed; either in The Anne Rowling Regenerative Neurology Clinic, at their own home, or at the University of Edinburgh.

Participants may be invited to take part in further assessments at the lab following completion of Phase 1 assessment if they have indicated on their Phase 1 consent form that they are willing to be contacted about further research.

Phase 2: Lab-Based Assessment

Participants who have completed Phase 1 testing who consent to be contacted about further research will be invited to the Visuomotor Laboratory at the University of Edinburgh to take part in more detailed tests (Phase 2), which will more fully investigate visuomotor and attentional deficits using eye-tracking and motion-tracking technology.

Participants will be invited to be tested on two separate two-hour sessions (with breaks), with the option of a 3rd further session.

Phase 3: Longitudinal Re-Assessment

Following completion of Phase 1 and 2 of the study, participants will be invited to Phase 3 (if they have indicated on their Phase 1 or Phase 2 consent form that they are willing to be contacted about further research).

Phase 3 of the study consists of longitudinal re-assessment of the participant on either the initial clinical screening tests (Phase 3A), the lab-based assesssments (Phase 3B), or both.

Participants who choose to take part in either or both of the Phase 3 assessments will be invited to do so 6 months after their initial involvement in Phase 1 or Phase 2.

Figure 1, displayed below, summarises the relationship between the different phases.

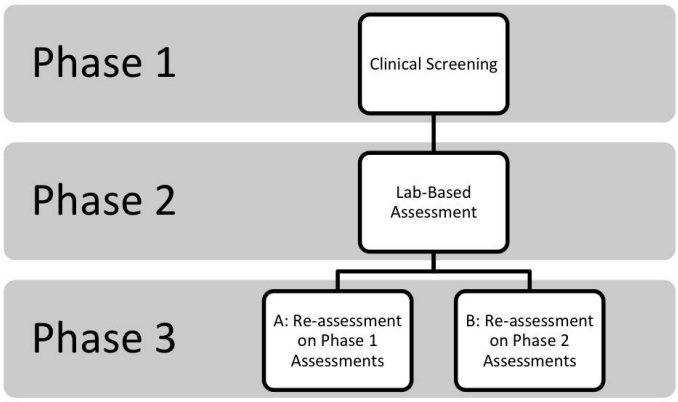

Figure 1: Study Phases

c. Recruitment & Consent

Participants will be recruited from The Anne Rowling Regenerative Neurology Clinic. Participants will be identified by their clinical care team as eligible for the study, and will be approached initially about the project at their routine clinical appointment by their treating clinician.

All participant invitation letters, participant information sheets, and newsletters will be made available as an audiovisual presentation through dedicated links provided with each form. This will enable participants who no longer maintain the ability to read to receive the information in an appropriate format. All the videos associated with the project will be hosted at "http://tinyurl.com/PCAproject".

This design feature of the project was discussed at a meeting for patients with PCA and their carers at the Anne Rowling Regenerative Neurology Clinic, Edinburgh, and it was decided that

providing online videos would be the best format for participants. In addition, participants who cannot read and write any longer as a function of disease progression will have the option to have their consent forms signed on their behalf with a witnessed signature. In addition, audio recordings of verbal consent will be taken from participants to ensure that full, informed consent was obtained for each participant prior to their enrolment in any of the project phases.

Participants who express an interest to their treating clinician in taking part in Phase 1 of the project will be sent a participant information sheet, a participant invitation letter, and a notification of interest form.

Participants who wish to take part after receiving this information will send their notification of interest form (in a stamped, addressed envelope provided) to the chief investigator, who will then contact them by their preferred method in order to set up the time and place for the Phase 1 test appointment.

Participants indicate on their consent form for Phase 1 whether they consent to be contacted about similar research, or lab-based research. Participants can indicate that they consent to either option, both, or neither.

If participants indicate that they are willing to be contacted with further information about similar research: they will be provided with information about Phase 3A after completing their Phase 1 test. A further summary of each phase of the study is provided below for clarity:

Phase 1 – Clinical Screening
Phase 2 – Lab-Based Assessment
Phase 3A – Longitudinal re-assessment on Phase 1 assessments
Phase 3B – Longitudinal re-assessment on Phase 2 assessments

If participants agree to receive information on both similar research and lab-based research, they will be sent information about Phase 2 following completion of the Phase 1 testing – and may be contacted again after completion of Phase 2 about Phase 3 testing. Similarly, participants will indicate on their consent form for Phase 2 if they consent to be contacted about taking part in repeat assessments (Phase 3). If they consent to be contacted with information about this kind of research: they will be contacted about Phase 3A or 3B testing following completion of their Phase 2 tests.

The possible participant pathways through the study and the information that will be sent to participants, contingent on their consent form preferences, are summarized in Figure 2, below.

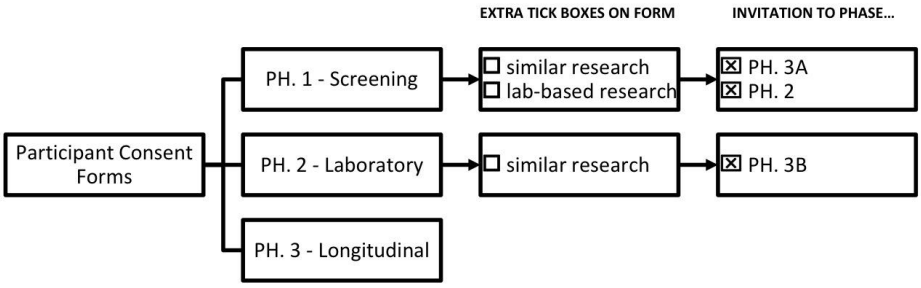

Figure 2: Participant Pathway (PH. = Phase)

At each stage of the project: participants will be provided with a new participant information sheet which details what would be involved for them, should they choose to take part in that given stage (Phase 1, 2, 3A and 3B), as well as receiving a new participant invitation letter. This is intended to ensure that participants are clear what they are being invited to take part in, and that they are aware that there is no obligation to continue with their participation in the research project beyond what they may have completed already.

Consent will be taken from participants before each phase of the project. Therefore, participants who consent to take part in Phase 1 are not automatically enrolled to take part in Phase 2, and participants who consent to take part in Phase 2 are not automatically enrolled to take part in Phase 3 testing.

Participants will be provided with contact information for the chief investigator, as well as contact information for an individual who is independent from the study. Their right to withdraw from the study at any time, without the necessity of providing a reason for doing so, will be made clear both on the study documentation which they receive, and verbally from the chief investigator at the point of consent for each phase.

d. Proposed Assessments

Phase 1: Clinical Screening

The assessments used in the clinical screening of participants include tests of higher visual functions as well as assessments of attention and language ability. These assessments will take up to

1.5 hours to complete. Participants will be given the opportunity to take frequent breaks, or to end the assessment at any time.

Participants can choose to be assessed in the Clinic, at their home, or at the University of Edinburgh. The proposed assessments are detailed in Table 1, below.

Table 1 Clinical Screening Assessments

Function	Assessment	Additional Test Descriptor	Time
Simultanagnosia	Navon Test	Letter Identification [17-20]	1 minute
Optic Ataxia	Touchscreen Pointing Task	[21]	2 minutes
Neglect	Touchscreen Cancellation Task	[21, 22]	2 minutes
Neglect	Line Bisection	[22]	3 minutes
Simultanagnosia / Neglect	BORB Test 1	Copying [23]	3 minutes
Simultanagnosia / Neglect	BORB Test 2-5	Matching [23]	6 minutes
Simultanagnosia / Neglect	Luria Test	Copying Luria Figures [24]	3 minutes
Simultanagnosia	BORB Test 6	Figure-Ground Segmentation [23]	3 minutes
Neglect	Apple Cancellation	Within- and between-object Neglect [25]	3 minutes
Apperceptive Visual Agnosia	BORB Test 7	Recognition Across Different Viewpoints [23]	3 minutes
Apperceptive Visual Agnosia	BORB Test 10	Object Decision [23]	3 minutes
Apperceptive Visual Agnosia	BORB Test 13-14	Picture Naming [23]	6 minutes
Finger Agnosia	Finger Agnosia Confrontation	Identify and name each finger	2 minutes
Sustained Attention	Test of Everyday Attention	Elevator Task (with distractor and switching) [26]	10 minutes
Apraxia	Maximum Tapping Rate	Dynamometer / Tapping Test	3 minutes
Hearing Ability	Performance Perceptual Test	Actual versus perceived hearing deficits	10 minutes
Language Functioning	Graded Naming Test	Object-naming ability	10 minutes
Aphasia	Test for Reception of Grammar	Understanding of Grammar	10 minutes

Phase 2: Lab-Based Assessment

Laboratory-based testing will consist of two sessions lasting up to 2 hours each (with breaks). A further 3rd testing session will be offered to participants who are keen to continue their involvement. Refreshments will be provided to participants at each testing session.

Psychophysical, motion-tracking and eye-tracking tasks will be conducted at the Visuomotor Laboratory of the University of Edinburgh. This facility is easily accessible for people with disabilities, and toilet and kitchen facilities are available for refreshment breaks.

The eye-tracking technology used are a pair of lightweight glasses with the eye-tracking technology in-built, therefore participants will have complete freedom of head movement and should not experience any discomfort.

Laboratory session 1: The aim of this session will be to quantify the core misreaching impairments of optic ataxia, and to test visuospatial attention under similar conditions, in order to evaluate the relationship between visuomotor and attentional symptoms. Details of assessments used in session 1 are summarised in Table 4, below.

Table 2: Laboratory Session 1 Assessments

Assessment Descriptor	Methodology Reference(s) Technique used
Pointing Task Pointing to visual targets presented at 6 locations in the horizontal plane under look-and-point, and point only instructions, with either hand. This will quantify any core misreaching deficit, and its modulation by hand, visual field, and retinal eccentricity. It will also provide measures of saccadic behaviour for comparison.	[27, 28] Combined eye-tracking (SMI goggles) and motion tracking (Optotrak Certus) with touch-screen tablet.
Grasping Task Grasping visual targets (Efron Blocks) at different locations in the horizontal and vertical plane, with either hand.	[29] Combined eye-tracking (SMI goggles) and motion tracking (Optotrak Certus) with Efron Blocks.
Matching Task Making estimates using Efron Blocks for hand-scaling and reaching to location.	[29] Combined eye-tracking (SMI goggles) and motion tracking (Optotrak Certus) with Efron Blocks.

Laboratory session 2: The aim of this session will be to examine and quantify the further features of optic ataxia, in order to evaluate whether these form a unitary syndrome, or dissociate across

participants. For each participant, the best and worst hand-field combination for pointing, determined in session 1, will be tested, alongside a free vision condition. Details of assessments used in session 2 are summarised in Table 5, below.

Table 3 Laboratory Session 2 Assessments

Assessment Descriptor	Methodology Reference(s) Technique used
Dual-Task Pointing Participants point to targets in the peripheral visual field while an attentionally demanding task is presented at the point of fixation.	[13] Combined eye-tracking (SMI goggles) and motion tracking (Optotrak Certus) with touch-screen tablet.
Dual-Task Contrast Sensitivity Determination of contrast sensitivity thresholds at 6 locations in the horizontal plane, with a concurrent attentionally demanting task presented at central fixation.	[29] Combined eye-tracking (SMI goggles) and motion tracking (Optotrak Certus) with touch-screen tablet.

Laboratory session 3: The aim of this additional session will be to investigate in greater detail the components of optic ataxia. This final session will be offered to participants who are keen to take part in further lab sessions.

Table 4 Laboratory Session 3 Assessments

Assessment Descriptor	Methodology Reference(s) Technique used
Attentional Window Comprehensive investigation into eye movements during scene exploration, by using a 'spotlight search' paradigm.	[30] Eyelink 1000 infra-red based eye tracker (no head restraint).

3. Materials

The materials used in each assessment for both Phase 1 and Phase 2 of the study are summarized in below. Please note that Phase 3A testing consists of repeating exactly the assessments used in Phase 1, and Phase 3B testing consists of repeating exactly the assessments used in Phase 2: therefore the materials used for each assessment are identical and have been omitted from this table for simplicity.

Phase 1: Clinical Screening

- Paper and pencil examiner marking sheets
- Touchscreen tablet computer
- Dynamometer

Phase 2: Laboratory Assessments

- SMI Eye-Tracking Goggles (CE declaration of conformity; EN55022:05/2008)
- Eyelink 1000 infra-red based eye tracker
- Optotrack Certus Motion Tracker
- Efron Blocks
- Touchscreen tablet computer

Proposed Analysis

Independent Analysis of Variance (ANOVA) tests will be used to measure the differences between groups (e.g. between PCA, PPA, CBD, and AD participants) on scores in the Phase 1 tests. Planned comparisons will be used to investigate differences between groups on subtests.

Kinematic analysis will be used to analyse the data from Phase 2 tests (eye- and motion-tracking data).

Practical Issues

There are no specific adverse effects, pain, discomfort, or risks to participants from taking part in this research. Phase 1 and Phase 3A testing involves using validated assessments which involve the participant using simple touchscreen or paper-and-pencil tests. Phase 2 and Phase 3B testing involves the participant coming to the Visuomotor Laboratory. These tests will involve the use of specialist eye- and motion-tracking technology which is calibrated for each individual and causes no discomfort.

The Visuomotor Laboratory is fully accessible.

Participants will be given the choice of testing location for Phase 1 and Phase 3A testing to minimize disruption and discomfort. They can choose to be tested at a pre-booked, private room in

The Anne Rowling Regenerative Neurology Clinic, at a pre-booked private room at the University of Edinburgh, or at their own home.

A further practical issue may be testing fatigue. Participants will be given frequent opportunities to take breaks, and refreshments will be provided for lab-based assessments.

Ethical Concerns

There are no ethical concerns associated with this project. Participants will be fully informed at the time of consent, and consent will be re-taken before each phase. Participants may withdraw from the study at any time.

Timescale

The time commitment associated with assessments for each phase is summarized in Table 7, below.

Table 5: Expected Involvement Time for Each Phase

Phase	Test Descriptor	Total Time Commitment
Phase 1	Clinical Screening Test (1 session)	1.5 hours
Phase 2	Lab-based Assessments (2 (or 3) separate sessions)	4 (or 6) hours
Phase 3A	Clinical Screening Test (1 session)	1.5 hours
Phase 3B	Lab-based Assessments (2 (or 3) separate sessions)	4 (or 6) hours

Participants are not obligated to take part in each phase (see Method sections parts 2.b. and 2.c. for details), therefore the total time participants spend being assessed will depend on which phases of the project they consent to take part in. All participants enrolled in the study will complete Phase 1 testing as a minimum, therefore the minimum time which participants will spend being assessed is 1.5 hours. The maximum amount of time a participant could spend being assessed, should they wish to take part in all four separate phases of the project, would be 11 hours.

If participants complete only Phase 1 testing – they would be engaged in the research for a total of around 1 week. This would be from the point of consent to the time of their appointment,

which would be made at the most convenient time for the participant approximately 1 week after their notification of interest form is received by the chief investigator. The minimum amount of time that a participant would be enrolled in the study would therefore be 1 week.

Participants who complete Phases 1, 2, and either 3A or 3B would be enrolled in the study for a total of around 6 months. This is because a 6 month delay would be necessary between completion of Phase 1 or 2 testing and the commencement of Phase 3A or 3B testing. The maximum amount of time that a participant would be enrolled in the study would therefore be 6 months.

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12.5 Appendix 5: Participant Invitation Letter (Phase 1)

THE UNIVERSITY *of* EDINBURGH

Anne Rowling
Regenerative Neurology Clinic

PARTICIPANT INVITATION LETTER
Phase 1

NOTICE FOR CARERS

To receive this information in video format, please visit **http://tinyurl.com/PCAproject** and select **Video 1.**

Understanding Vision and Movement Changes in Neurodegenerative Disease

Dear

This letter is being sent to you by your clinical care team at The Anne Rowling Regenerative Neurology Clinic on behalf of Miss Harriet Ingle, a researcher based at the University of Edinburgh.

We are writing to you to invite you to participate in a research study. We are approaching you because you have a neurodegenerative disease, and you have been identified by your clinical care team as having some of the symptoms which we are interested in investigating.

We have enclosed a 'Participant Information Sheet' for you to read. This gives more information about the study and it's aims, as well as what would be involved if you chose to take part. Please take some time to read this before you decide whether you'd like to take part.

If you would like to take part – then please use the 'Notification of Interest' form and the stamped, addressed envelope which are both enclosed. Alternatively, you can use the contact details in the box below. If we do not hear back from you within 2 weeks of receiving this letter, then we'd like to get in touch to check whether you're interested or not, and to answer any questions that you might have.

Miss Harriet Ingle is the lead researcher on this study, and is happy to answer any questions that you, or your partner or carer, may have. If you would like to meet Harriet in person before you decide whether or not to take part – then please contact her using the details in the box below and she can arrange to come and visit you at your home or any preferred location to talk about the project.

Thank you very much for taking the time to read this information.

Yours sincerely,

Miss Harriet Ingle
PhD Researcher

If you have any questions about the study, or if you'd like to tell us that you want to take part then please contact:

Miss Harriet Ingle (PhD Researcher)
Email: **h.e.ingle@sms.ed.ac.uk**, Phone: **07751 601 069**,
Address: **Miss H. Ingle, The University of Edinburgh, Psychology Building, 7 George Square, Room S35, Edinburgh, EH8 9JZ.**

If you'd like to speak to anyone else about the study, an independent contact is:

Professor Sharon Abrahams
Email: **s.abrahams@ed.ac.uk**, Phone: **0131 650 3339**

12.6 Appendix 6: Participant Information Sheet (Phase 1)

THE UNIVERSITY *of* EDINBURGH

Anne Rowling
Regenerative Neurology Clinic

PARTICIPANT INFORMATION SHEET
Phase 1

NOTICE FOR CARERS

To receive this information in video format, please visit **http://tinyurl.com/PCAproject** and select **Video 2.**

Understanding Vision and Movement Changes in Neurodegenerative Disease

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish.

Part 1 tells you the purpose of the study, and what will happen if you take part.

Part 2 gives you more detailed information about the conduct of the study.

Please take the time to read the following information carefully. Please feel free to contact us if there is anything that is not clear, or if you would like more information.

Part 1
The purpose of the study and what to expect.

What is the purpose of the study?

We want to understand more about the visual symptoms and movement problems which can occur in people with some neurodegenerative diseases. The aim of this research is to understand better the symptom profile of different neurodegenerative diseases and to develop a method to test for these symptoms early.

Why have I been asked to take part?

You have been invited to take part as you have been identified by your clinical care team as having some of the symptoms which we are interested in investigating.

Do I have to take part?

No, it is up to you to decide to join the study. This information sheet should give you all the information you need, but you can also contact us to ask any further questions that you might have. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen if I take part?

If you choose to take part then you will be asked to sign a consent form. This form tells us that you want to take part in the research project. The form will also tell us whether you are happy to be contacted about any further studies that we might be running, and whether you are happy for a member of your clinical care team to access your medical records. You can choose whether you're happy for your GP to be notified of your participation in this research project.

You will then arrange to meet the researcher, Harriet Ingle, who will test your vision, hand-eye co-ordination, and listening ability using a range of different tests: some of them on a touch-screen computer, and some of them will be paper-and-pencil. These tests will take around 1.5 hours to complete.

The researcher will explain to you how to do each of the tests and is happy to answer any questions you might have, so don't worry if you haven't participated in a research project before. You'll be given the opportunity to take breaks or to stop the tests at any time.

You will agree with the researcher where you would like these tests to take place. You can choose for them to happen at the Anne Rowling Clinic, at your home, or at the University of Edinburgh.

Your travel costs to meet the researcher will be compensated.

After this you might be sent further information about similar research projects, but only if you have indicated that it is okay to contact you by signing that box on your consent form.

What are the possible benefits of taking part?

There are no direct benefits to you in taking part.

However, the information that we get from this study will help to improve the treatment and diagnosis of people with Posterior Cortical Atrophy (PCA), Corticobasal Degeneration, and other related neurodegenerative diseases.

We hope to develop a new way to check for symptoms of these diseases so that they can be diagnosed faster.

What are the possible disadvantages and risks of taking part?

We do not anticipate any risks from involvement in this study.

One disadvantage of taking part in this study is that, for some people, it may be tiring to complete the tests.

Part 2
The conduct of the study and how to find further information.

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any time without giving a reason. This will not affect the healthcare that you receive.

If you have to withdraw from the study for health reasons, we would like to use the data that we have already collected for our analysis. It is up to you whether this happens, or whether the data is destroyed.

What will happen with the results of the study?

The results of this study may be published in the form of conference documentation, scientific journals, or academic writing.

You will be given the opportunity to find out more about the overall findings of the study once it has been completed.

The data collected as part of this study will be stored in a locked, private, University of Edinburgh office and will be fully anonymised. Data will only be accessible by members of the research team. All data, including voice recordings, will be stored for 3 years after the study has ended in order to comply with the UKRIO Code of Practice for Research which the University of Edinburgh implements.

Will my participation be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorized persons who are directly involved in the research, or who form part of your clinical care team. Any person who looks at this information will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

Who is organising the research and why?

This research project is jointly funded by the University of Edinburgh Psychology Department and Alzheimer Scotland Dementia Research Centre. This research is being conducted as part of a PhD study in Experimental Neuropsychology.

Who has reviewed the study?

All research in the NHS is looked at by independent groups of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by South East Scotland Research Ethics Committee 01, and a favourable ethical opinion has been obtained (Reference: 15/SS/068).

Further information and contact details

Please use the appropriate contact from the box below.

For questions about the study please contact either:

Miss Harriet Ingle (PhD Researcher)
Email: **h.e.ingle@sms.ed.ac.uk**, Phone: **07751 601 069**

If you'd like to speak to anyone else about the study, an independent contact is:

Professor Sharon Abrahams
Email: **s.abrahams@ed.ac.uk**, Phone: **0131 650 3339**

If you wish to make a complaint about the study please contact NHS Lothian:

NHS Lothian Complaints Team
Email: complaints.team@nhslothian.scot.nhs.uk, Phone: 0131 465 5708, Address: NHS Lothian Complaints Team, 2nd Floor, Waverley Gate, 2-4 Waterloo Place, Edinburgh, EH1 3EG

12.7 Appendix 7: Notification of Interest Form

Notification of Interest Form: General, Version 1.4, 12.05.15

THE UNIVERSITY *of* EDINBURGH

Anne Rowling
Regenerative Neurology Clinic

NOTIFICATION OF INTEREST FORM
Notification of Interest in Participation

Understanding Vision and Movement Changes in Neurodegenerative Disease

Name: _____

Address: _____

_____

_____

Postcode: _____

Telephone: _____

Alternative Contact: _____

1. I am interested in participation in the above project — YES / NO

2. I agree for the lead researcher to contact me to arrange further discussions and potentially a date and time to be assessed. — YES / NO

PLEASE RETURN IN THE ENVELOPE PROVIDED

Page 1 of 1

12.8 Appendix 8: Participant Invitation Letter (Phase 2)

THE UNIVERSITY *of* EDINBURGH

Anne Rowling
Regenerative Neurology Clinic

PARTICIPANT INVITATION LETTER
Phase 2

NOTICE FOR CARERS

To receive this information in video format, please visit **http://tinyurl.com/PCAproject** and select **Video 3.**

Understanding Vision and Movement Changes in Neurodegenerative Disease

Dear

This letter is being sent to you by your clinical care team at The Anne Rowling Regenerative Neurology Clinic on behalf of Miss Harriet Ingle, a researcher based at the University of Edinburgh.

We are writing to you to thank you for taking part in Phase 1 of our research study about neurodegenerative diseases, and to invite you to take part in a new study.

The research that we are conducting is giving a valuable insight into some of the visual symptoms that people experience with certain neurodegenerative diseases. We'd like to build on the results from the first part of our study, which is why we would like to invite you to take part in Phase 2.

We are approaching you because you have already taken part in our first research study, Phase 1. In that study Miss Harriet Ingle (the lead researcher) met you and did some different tests on your vision, language ability, and hand-eye coordination.

This next study, Phase 2, tests the same things but uses more advanced techniques in order to gain more information.

We have enclosed a 'Participant Information Sheet' for you to read. This gives more information about this new study and it's aims, as well as what would be involved if you chose to take part. Please take some time to read this before you decide whether you'd like to take part.

If you would like to take part – then please use the 'Notification of Interest' form and the stamped, addressed envelope which are both enclosed.

Alternatively, you can use the contact details in the box on the back of this sheet. If we do not hear back from you within 2 weeks of receiving this letter, then we'd like to get in touch to check whether you're interested or not, and to answer any questions that you might have.

You can feel free to contact Harriet using the details on the back of this sheet if you have any questions, or if you would like to find out more information.

Thank you very much for taking the time to read this information.

Yours sincerely,

Miss Harriet Ingle
PhD Researcher

If you have any questions about the study, or if you'd like to tell us that you want to take part then please contact:

Miss Harriet Ingle (PhD Researcher)
Email: **h.e.ingle@sms.ed.ac.uk**, Phone: **07751 601 069**,
Address: **Miss H. Ingle, The University of Edinburgh, Psychology Building, 7 George Square, Room US46, Edinburgh, EH8 9JZ.**

If you'd like to speak to anyone else about the study, an independent contact is:

Professor Sharon Abrahams
Email: **s.abrahams@ed.ac.uk**, Phone: **0131 650 3339**

12.9 Appendix 9: Participant Information Sheet (Phase 2)

THE UNIVERSITY *of* EDINBURGH

Anne Rowling
Regenerative Neurology Clinic

PARTICIPANT INFORMATION SHEET
Phase 2

NOTICE FOR CARERS

To receive this information in video format, please visit **http://tinyurl.com/PCAproject** and select **Video 4.**

Understanding Vision and Movement Changes in Neurodegenerative Disease

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish.

Part 1 tells you the purpose of the study, and what will happen if you take part.

Part 2 gives you more detailed information about the conduct of the study.

Please take the time to read the following information carefully. Please feel free to contact us if there is anything that is not clear, or if you would like more information.

Part 1
The purpose of the study and what to expect.

What is the purpose of the study?

We want to understand more about the visual symptoms and movement problems which can occur in people with some neurodegenerative diseases. The aim of this research is to understand better the symptom profile of different neurodegenerative diseases and to develop a method to test for these symptoms early.

Why have I been asked to take part?

You have been invited to take part as you have been identified by your clinical care team as having some of the symptoms which we are interested in investigating.

You have already taken part in one of our research studies. In that study you met Harriet Ingle, the PhD researcher, and she tested your vision, listening ability, and hand-eye-coordination using a touch-screen computer and paper-and-pencil tests.

This new study that you are being invited to aims to look at similar things, but in greater detail using specialist eye-tracking and motion-tracking technology. This technology is based at the University of Edinburgh. It is kept in a specialist laboratory used for this kind of research.

Do I have to take part?

No, it is up to you to decide to join the study. This information sheet should give you all the information you need, but you can also contact us to ask any further questions that you might have. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen if I take part?

If you choose to take part then you will be asked to sign a consent form. This form tells us that you want to take part in the research project. The form will also tell us whether you are happy to be contacted about any further studies that we might be running, and whether you are happy for a member of your clinical care team to access your medical records. You can choose whether you're happy for your GP to be notified of your participation in this research project.

You will then arrange to meet the researcher, Harriet Ingle, at the University of Edinburgh. You will be invited to be tested on two separate sessions. Each testing session will take around 2 hours to complete. These will happen on different days,

which you'll arrange in advance with the researcher. In total, you'll complete 4 hours worth of tests if you choose to take part.

The researcher will test you using a range of very simple pointing and reaching tasks. Using eye-tracking and motion-tracking technology, we will be able to get very detailed information about your vision and hand-eye-coordination.

The researcher will explain to you how to do each of the tests and is happy to answer any questions you might have. You'll be given the opportunity to take breaks or to stop the tests at any time.

These tests will take place at the Visuomotor Laboratory at the University of Edinburgh.

Your travel costs to meet the researcher will be compensated.

After this you might be sent further information about similar research projects, but only if you have indicated that it is okay to contact you by signing that box on your consent form.

What are the possible benefits of taking part?

There are no direct benefits to you in taking part.

However, the information that we get from this study will help to improve the treatment and diagnosis of people with Posterior Cortical Atrophy (PCA), Corticobasal Degeneration, and other related neurodegenerative diseases.

We hope to develop a new way to check for symptoms of these diseases so that they can be diagnosed faster.

Using eye-tracking and motion-tracking technology we will be able to get much more detailed information about these symptoms than we can with other tests.

What are the possible disadvantages and risks of taking part?

We do not anticipate any risks from involvement in this study.

One disadvantage of taking part in this study is that, for some people, it may be tiring to complete the tests.

The eye-tracking and motion-tracking equipment will be calibrated for use with each individual by an experienced researcher. This equipment is in contact with your body, but does not cause any discomfort.

This study involves travelling to the University of Edinburgh to be tested in the Visuomotor laboratory on two separate occasions. Each visit should take no longer than

2 hours, therefore you will be tested for a total of 4 hours. The tests are very simple, although some people might find the testing session a little tiring. You will be offered the chance to take breaks, and refreshments will be provided.

Part 2
The conduct of the study and how to find further information.

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any time without giving a reason. This will not affect the healthcare that you receive.

If you have to withdraw from the study for health reasons, we would like to use the data that we have already collected for our analysis. It is up to you whether this happens, or whether the data is destroyed.

What will happen with the results of the study?

The results of this study may be published in the form of conference documentation, scientific journals, or academic writing.

You will be given the opportunity to find out more about the overall findings of the study once it has been completed.

The data collected as part of this study will be stored in a locked, private, University of Edinburgh office and will be fully anonymised. Data will only be accessible by members of the research team. All data, including voice recordings, will be stored for 3 years after the study has ended in order to comply with the UKRIO Code of Practice for Research which the University of Edinburgh implements.

Will my participation be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorized persons who are directly involved in the research, or who form part of your clinical care team. Any person who looks at this information will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

Who is organising the research and why?

This research project is jointly funded by the University of Edinburgh Psychology Department and Alzheimer Scotland Dementia Research Centre. This research is being conducted as part of a PhD study in Experimental Neuropsychology.

Who has reviewed the study?

All research in the NHS is looked at by independent groups of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by South East Scotland Research Ethics Committee 01, and a favourable ethical opinion has been obtained (Reference: 15/SS/068).

Further information and contact details

Please use the appropriate contact from the box below.

For questions about the study please contact either:

Miss Harriet Ingle (PhD Researcher)
Email: **h.e.ingle@sms.ed.ac.uk**, Phone: **07751 601 069**

If you'd like to speak to anyone else about the study, an independent contact is:

Professor Sharon Abrahams
Email: **s.abrahams@ed.ac.uk**, Phone: **0131 650 3339**

If you wish to make a complaint about the study please contact NHS Lothian:

NHS Lothian Complaints Team
Email: complaints.team@nhslothian.scot.nhs.uk, Phone: 0131 465 5708, Address: NHS Lothian Complaints Team, 2nd Floor, Waverley Gate, 2-4 Waterloo Place, Edinburgh, EH1 3EG

12.10 Appendix 10: Consent Form (Phase 1)

PARTICIPANT CONSENT FORM
Phase 1

Understanding Vision and Movement Changes in Neurodegenerative Disease

PLEASE INITIAL BOX

1. I confirm that I have read and understood, or watched 'Video 2' and understood the information sheet (Version 1.3, 24.03.15) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of data collected during the study may be looked at by individuals from the regulatory authorities and from the Sponsor(s) (NHS Lothian and the University of Edinburgh) where it is relevant to my taking part in this research. I give permission for those individuals to have access to my data. **No identifiable information will be given to third parties.** ☐
4. I understand that I will not benefit financially from taking part in this study. ☐
5. I agree to take part in the above study. ☐
6. I agree that my GP can be informed that I am taking part in this study. ☐

Name of participant: _____ Date: _____

Signature: _____ Date: _____

Where the participant is physically unable to sign a witness can complete the form and sign on their behalf as long as the witness is satisfied that the participant has understood the information sheet and the consent form.

Name of witness: _____ Date: _____

Signature of witness: _____ Date: _____

Name of person taking consent: _____ Date: _____

Signature of person taking consent: _____ Date: _____

Audio recording of consent:

I agree to be contacted with information for more detailed follow-up testing at the University of Edinburgh. ☐

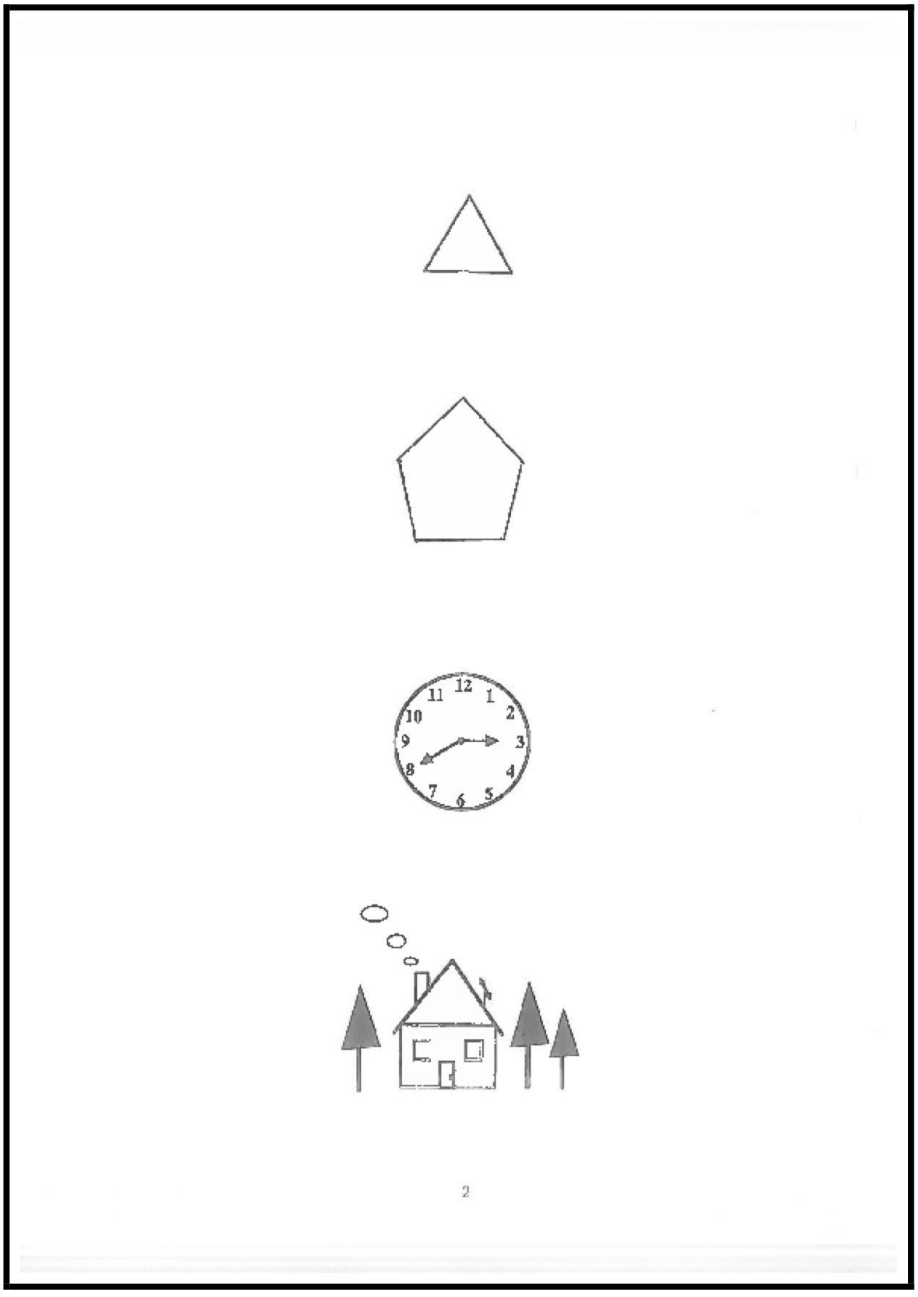
I agree to be contacted for a follow-up test session in 6-12 months. ☐

COPIES OF FORMS:

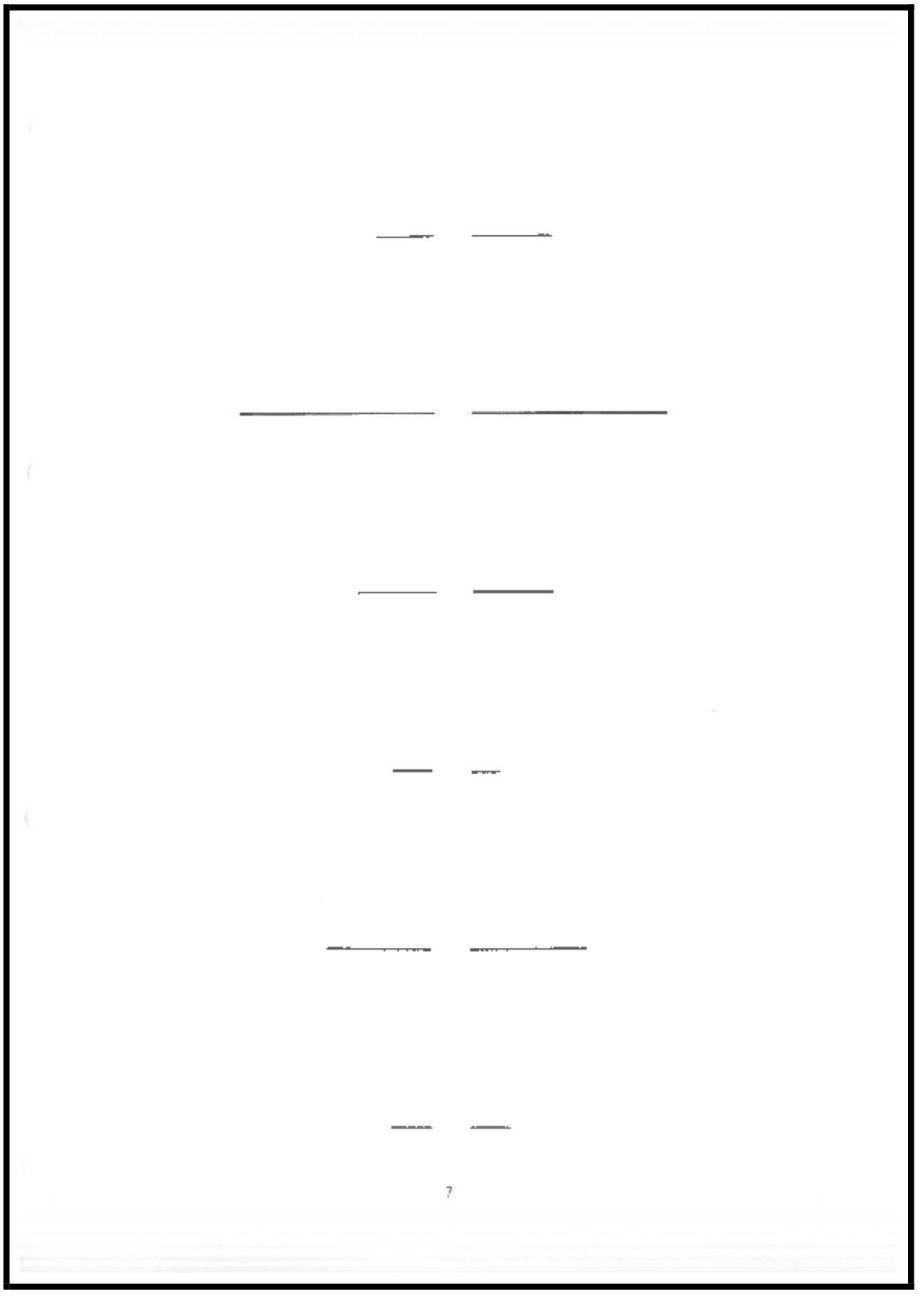
Original (x1) to be retained at University of Edinburgh. Copy (x1) to be retained by the participant.

12.11 Appendix 11: BORB Test Materials

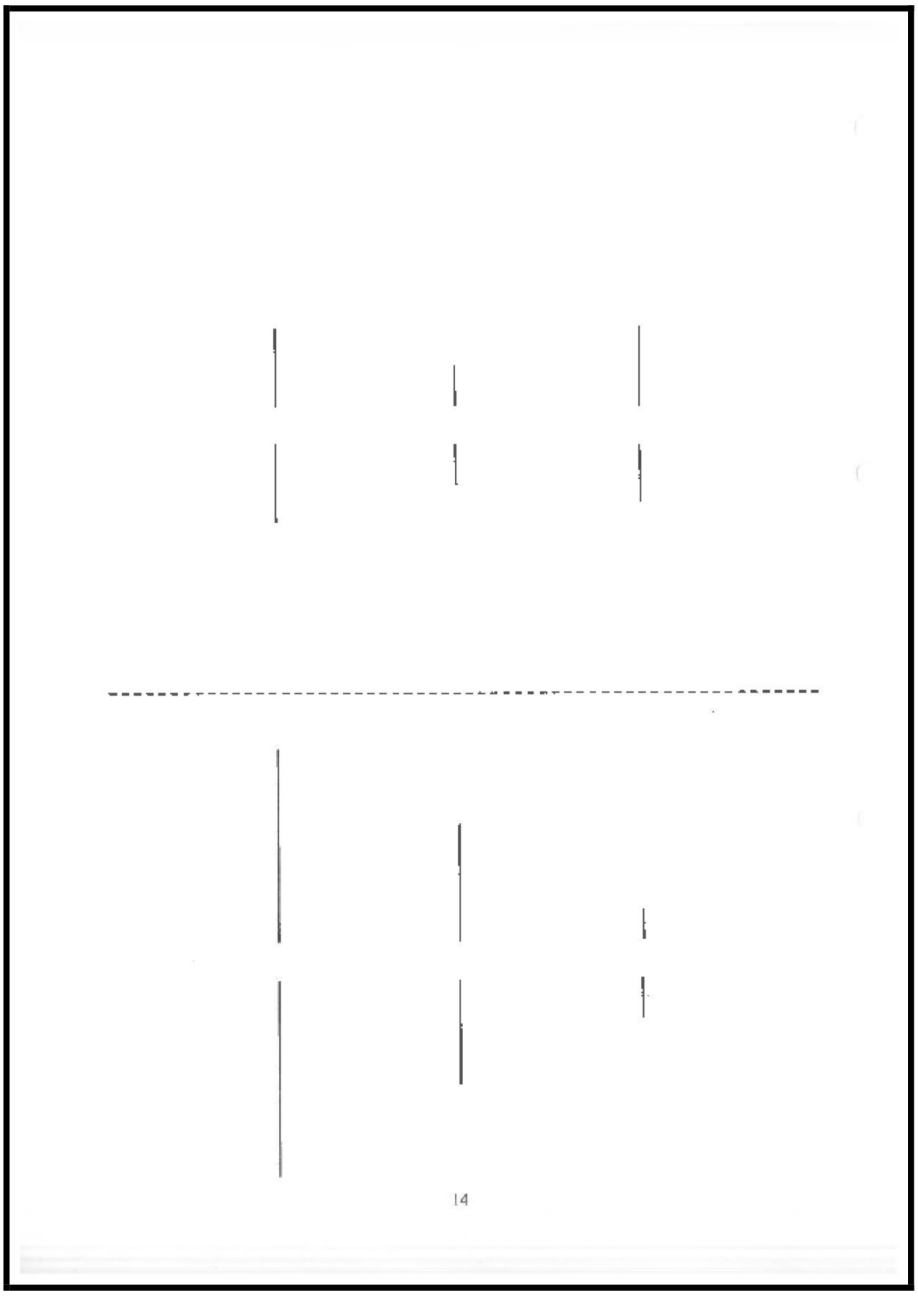
BORB 1 – Copying of Elementary Shapes



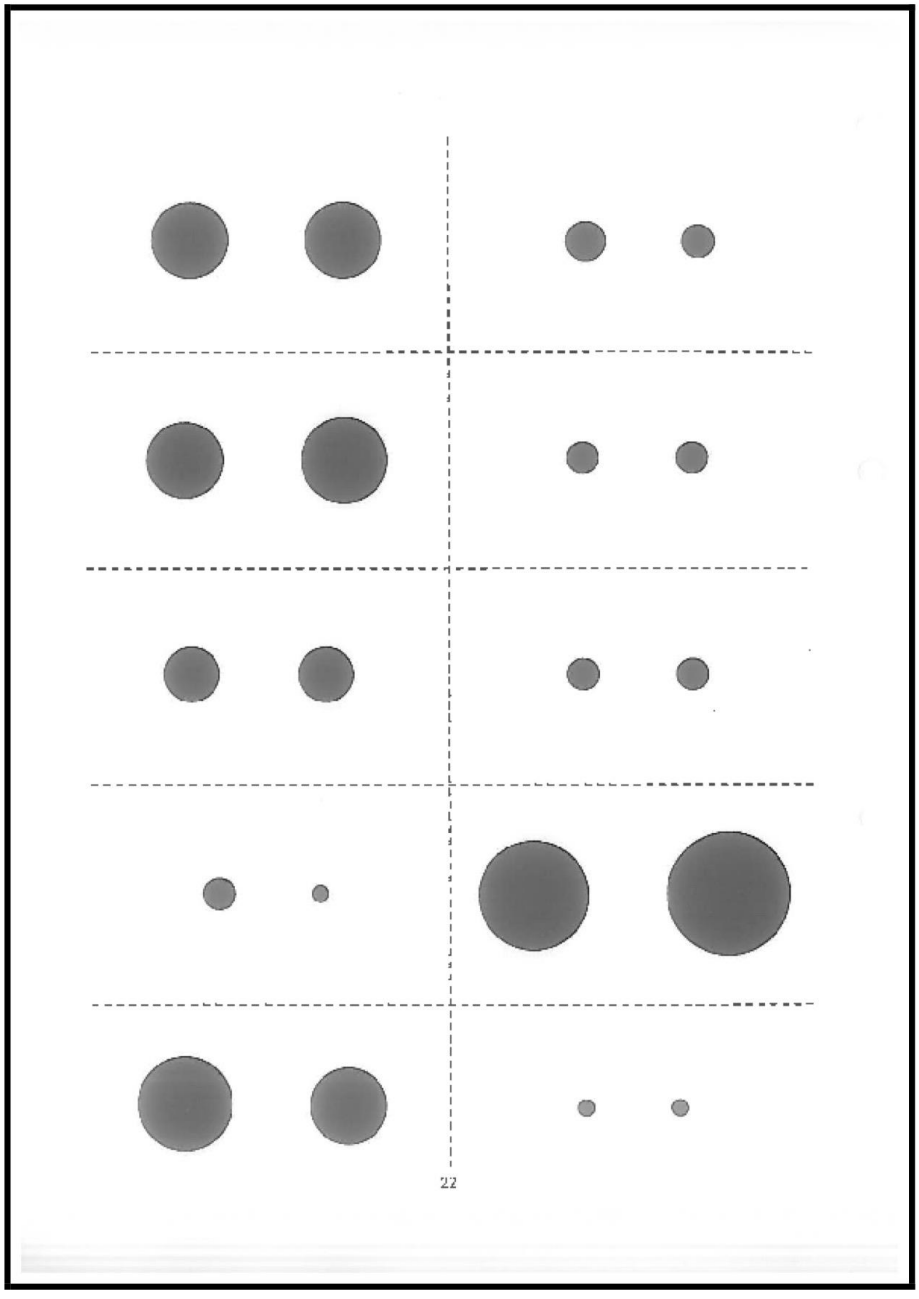
BORB 2A – Line Length



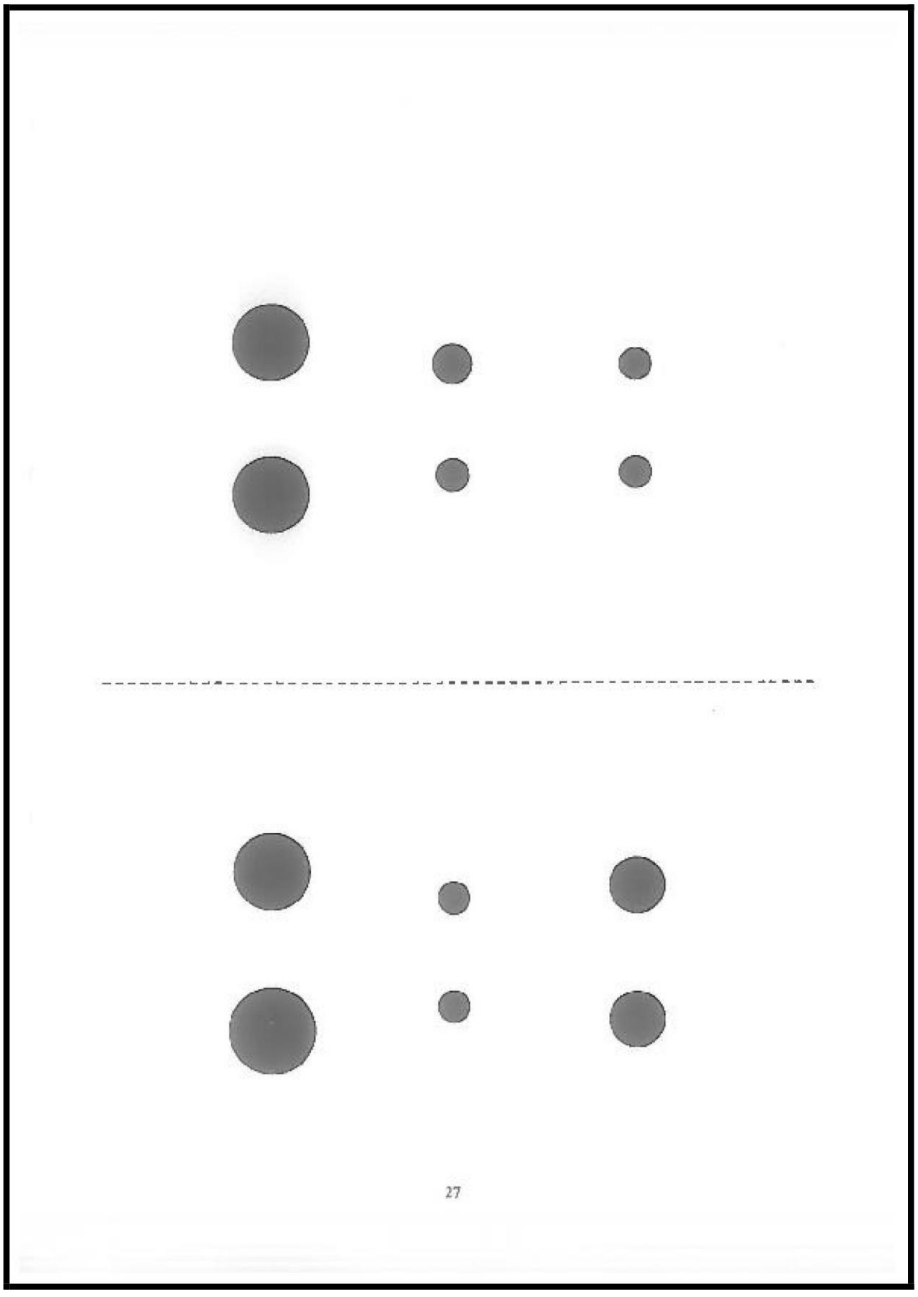
BORB 2B – Line Length (alternative version when neglect is suspected)



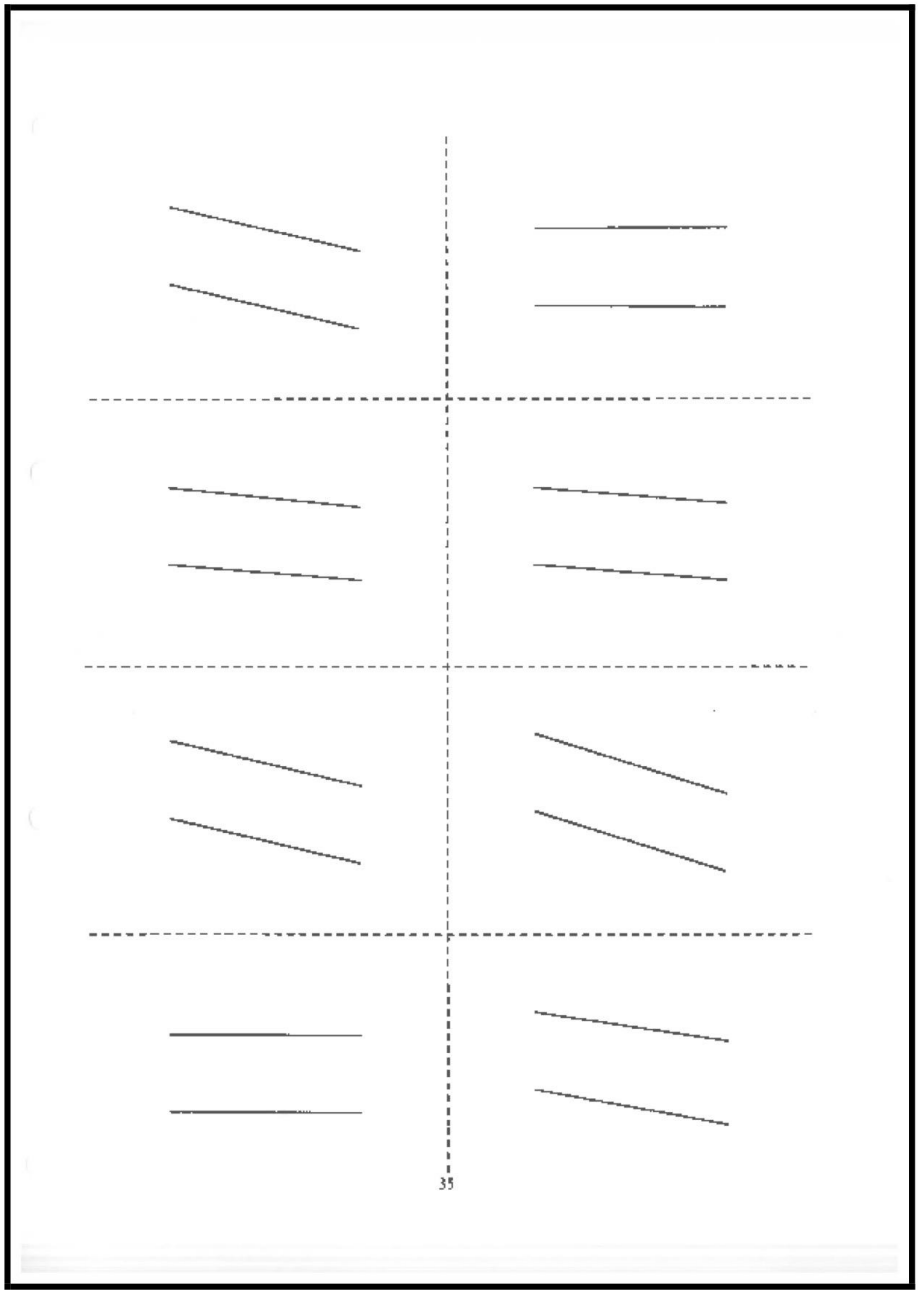
BORB 3A – Stimulus Size



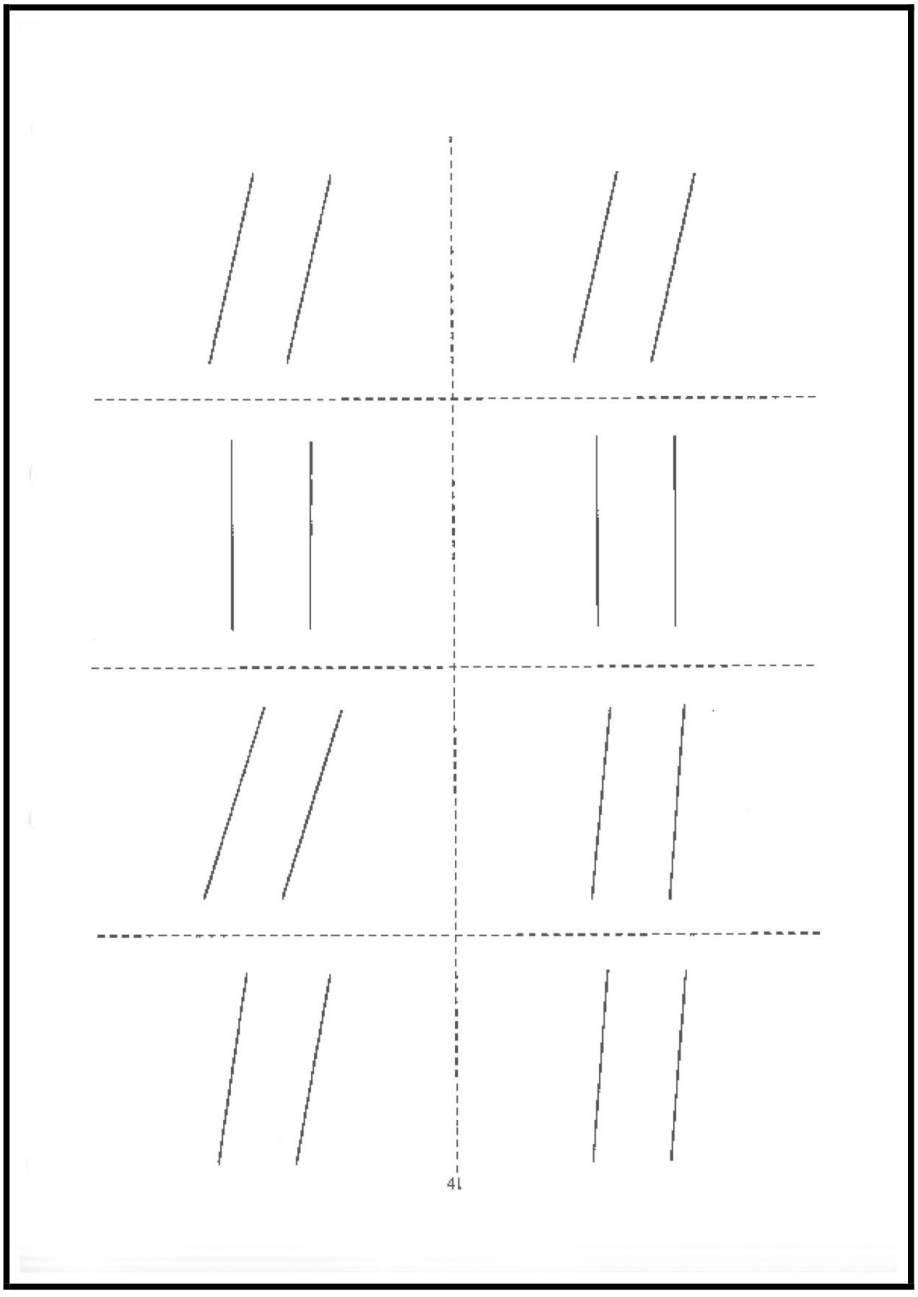
BORB 3B – Stimulus Size (alternative version when neglect is suspected)



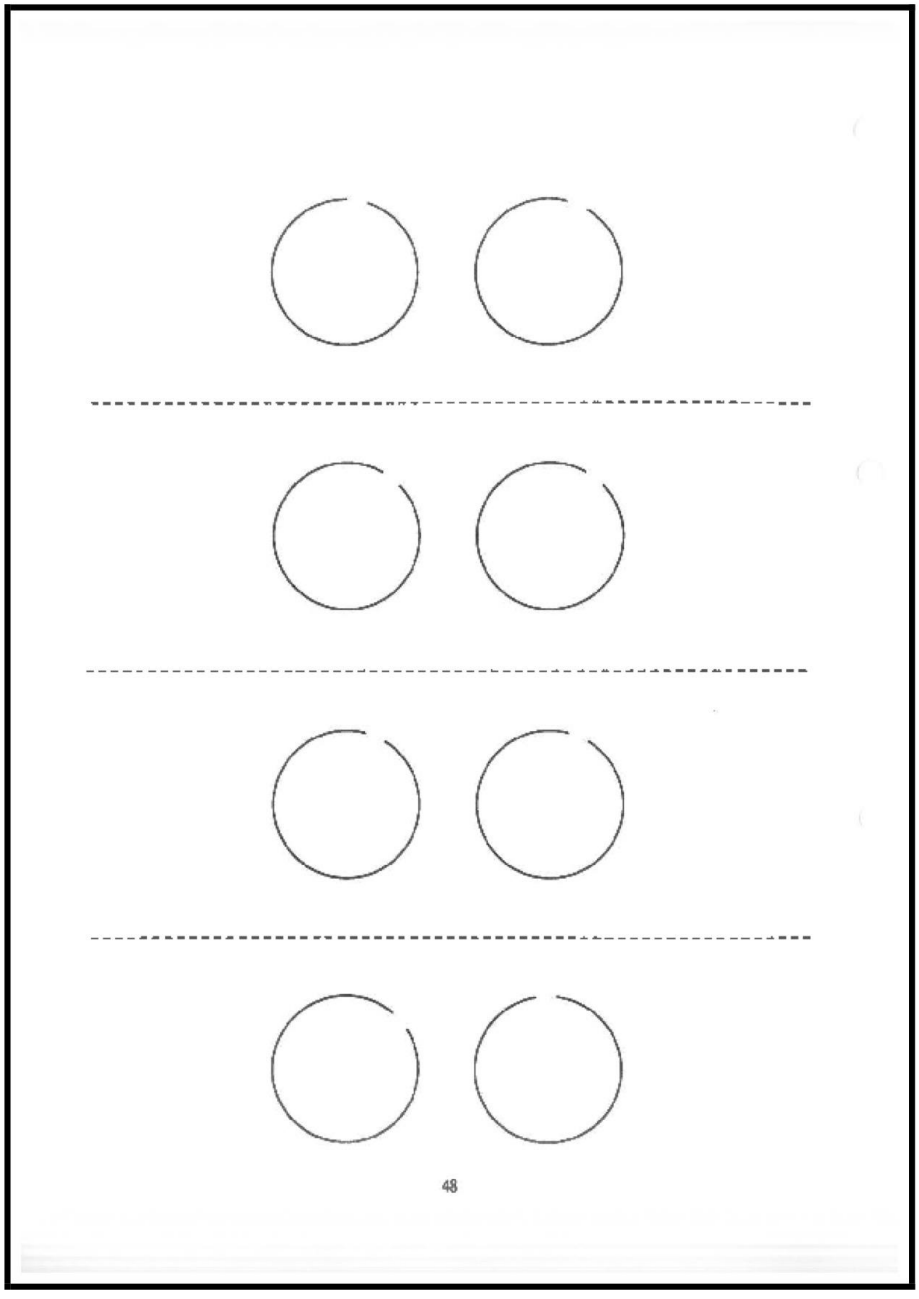
BORB 4A – Line Orientation



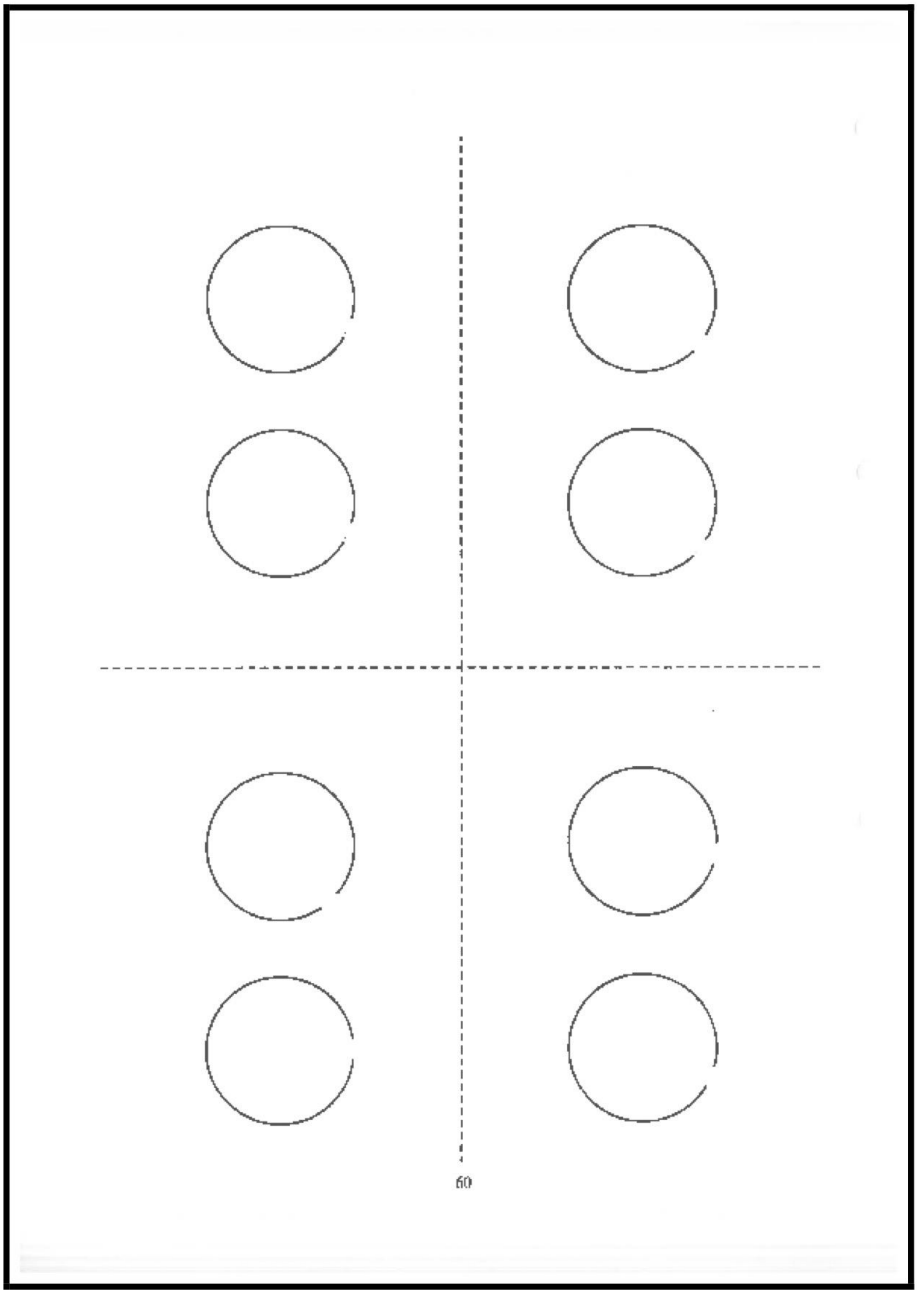
BORB 4B – Line Orientation (alternative version when neglect is suspected)



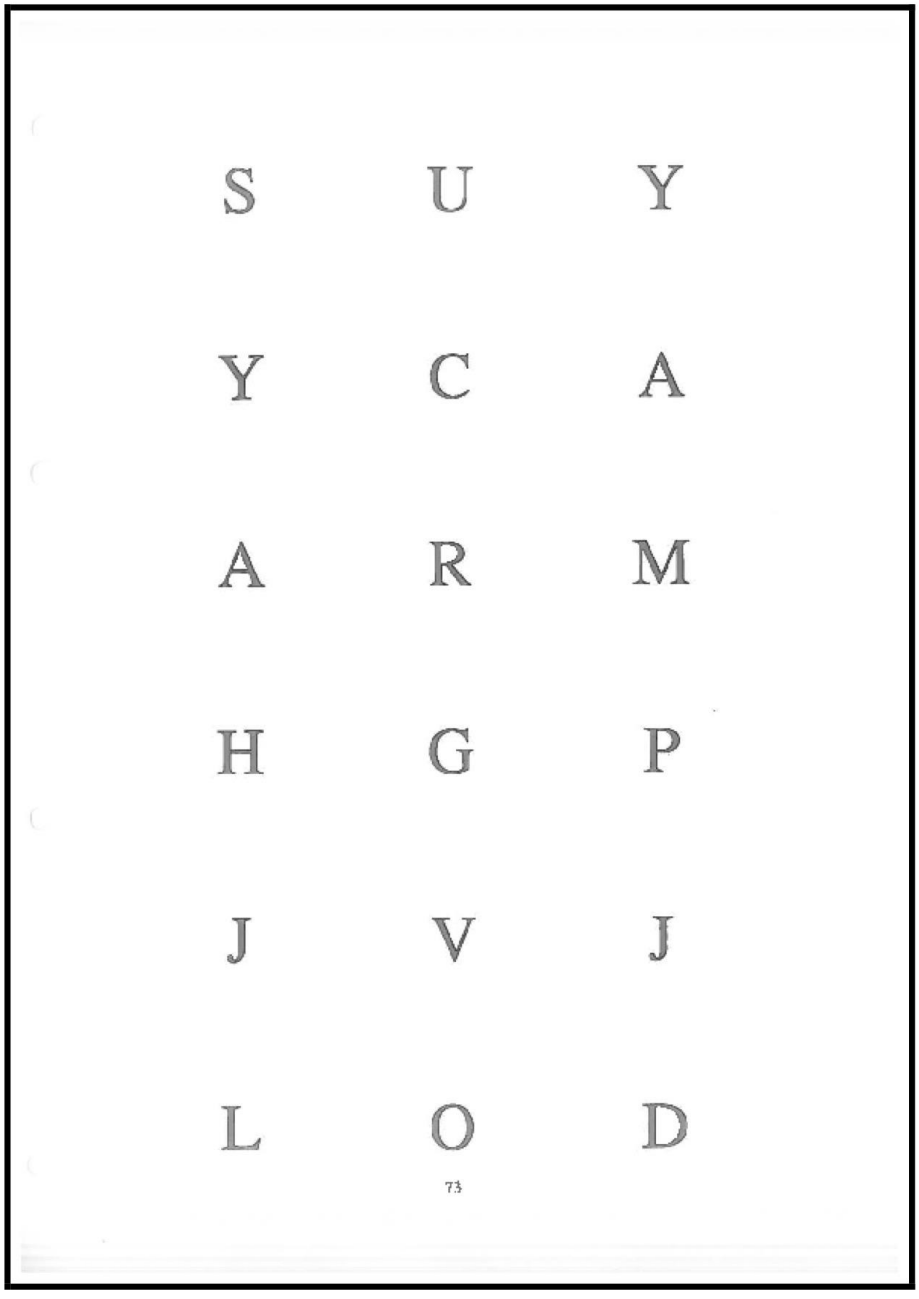
BORB 5A – Position of Gap



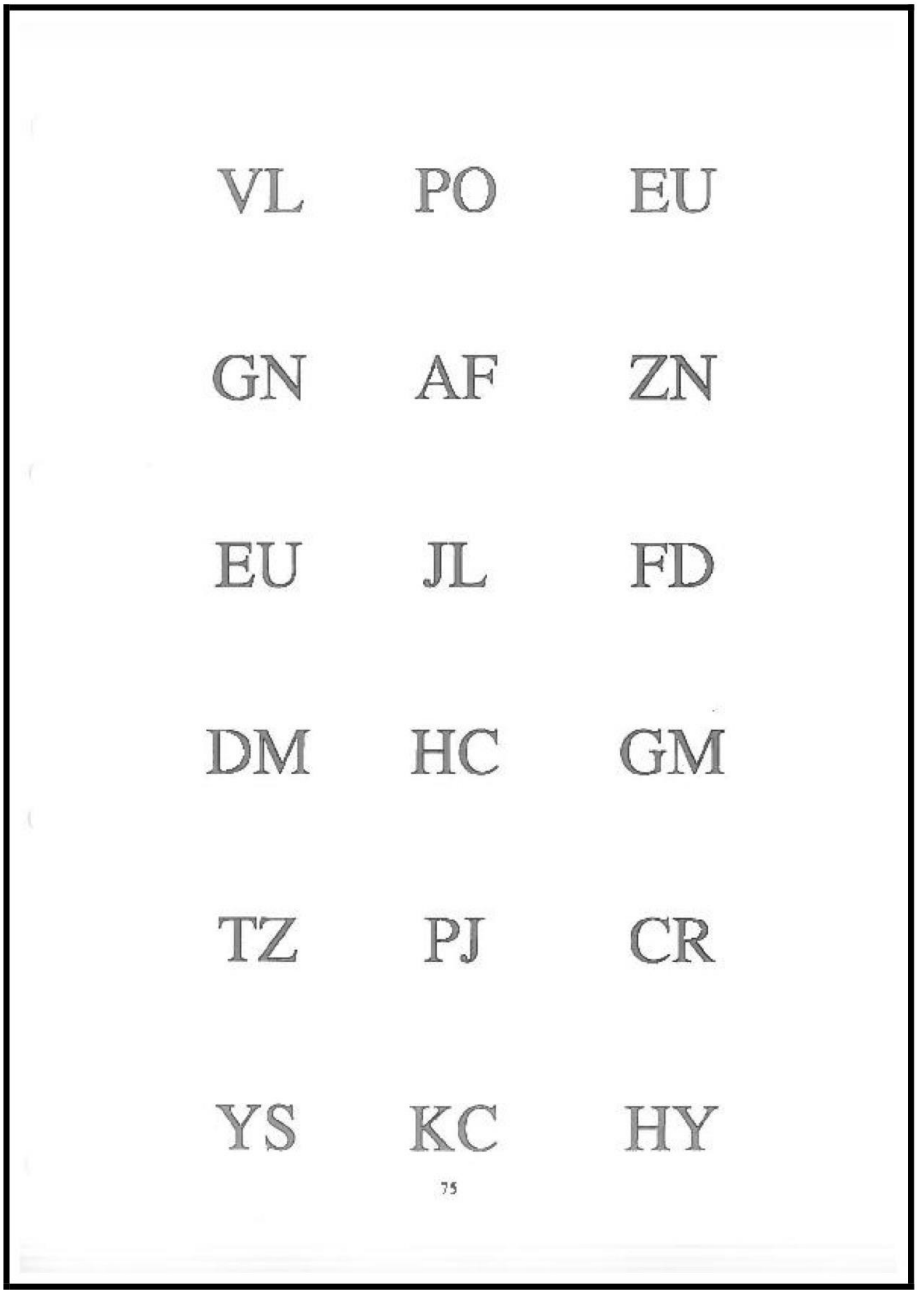
BORB 5B – Position of Gap (alternative version when neglect is suspected)



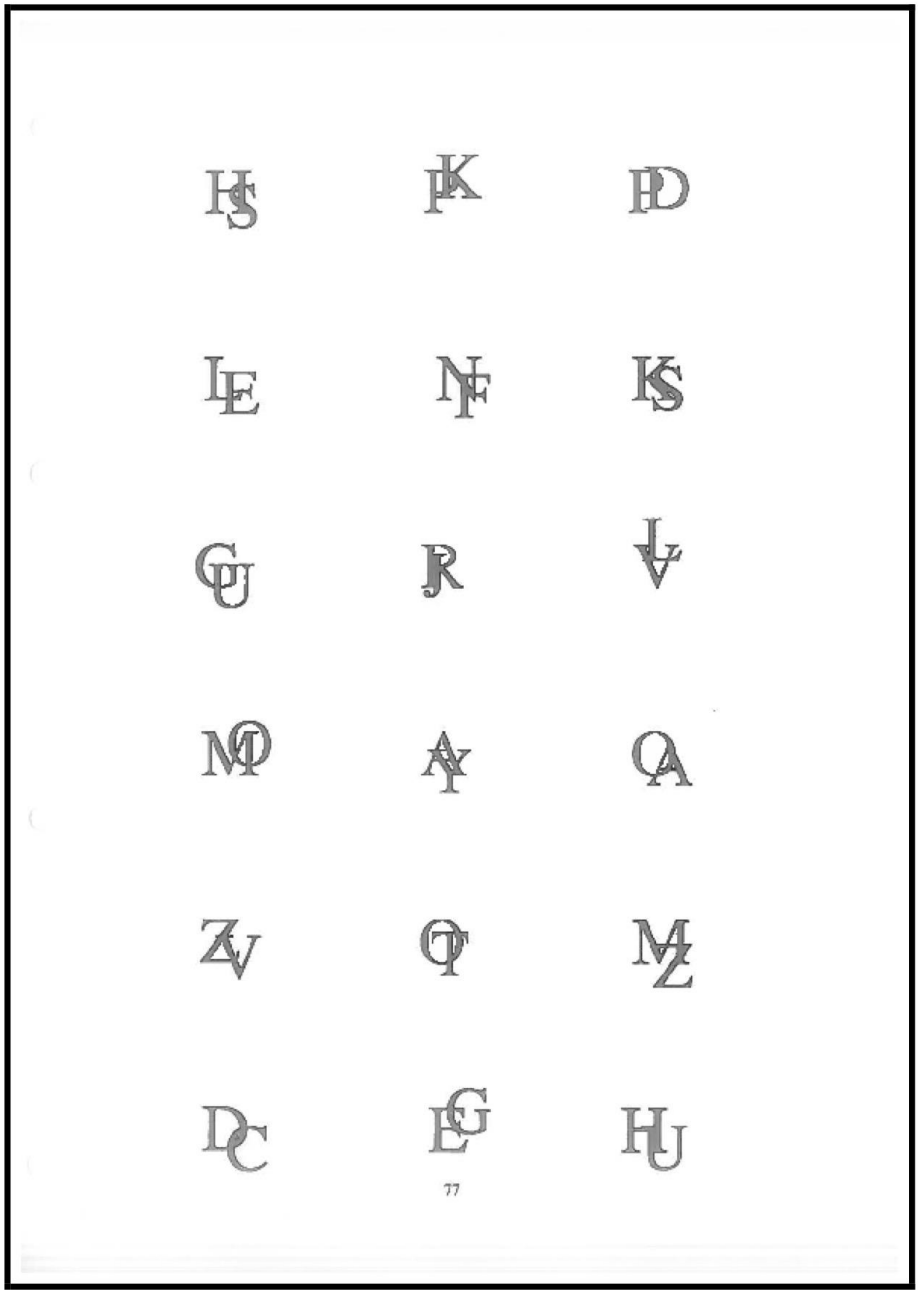
BORB 6 – Letters Single



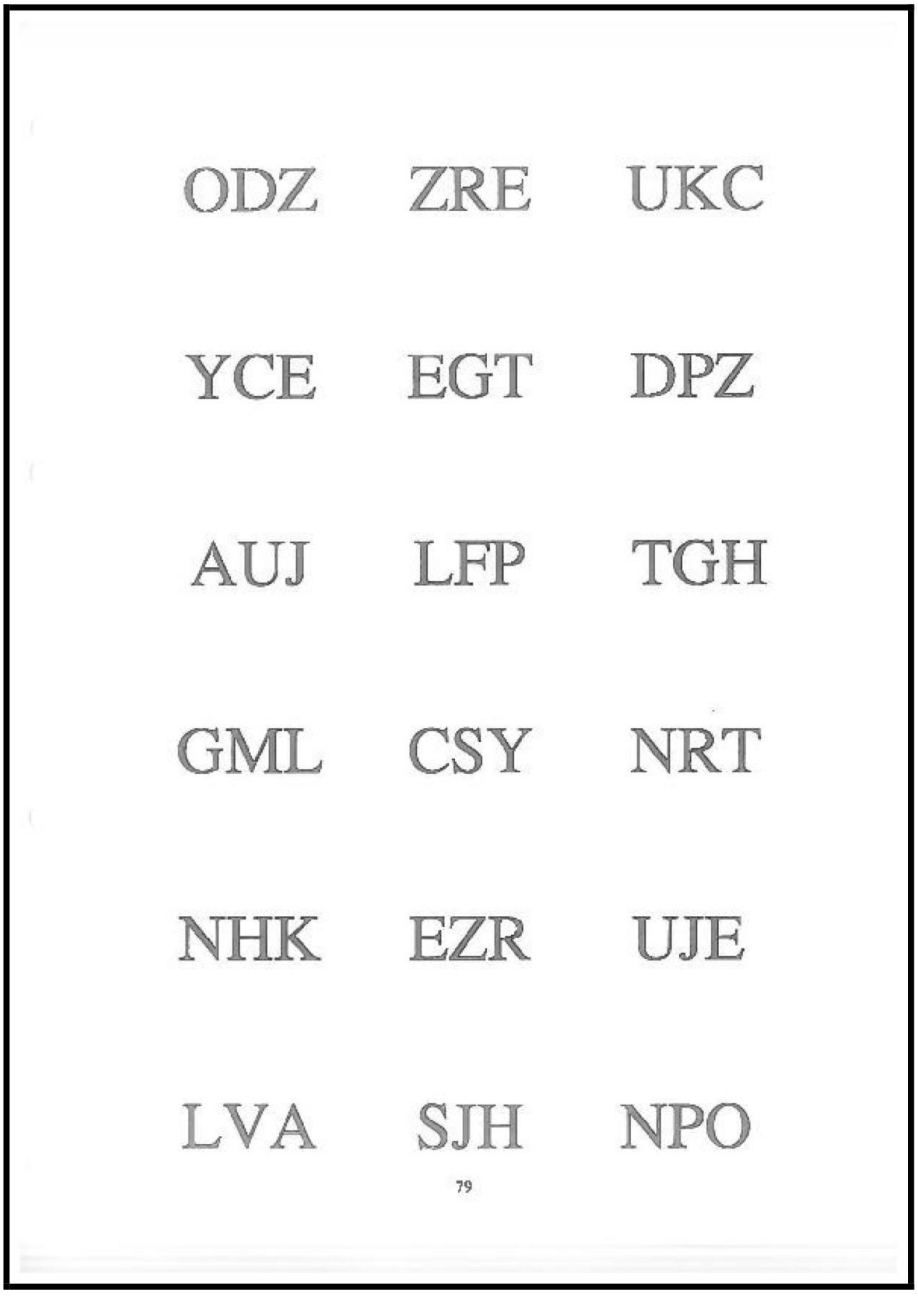
BORB 6 – Letters Paired



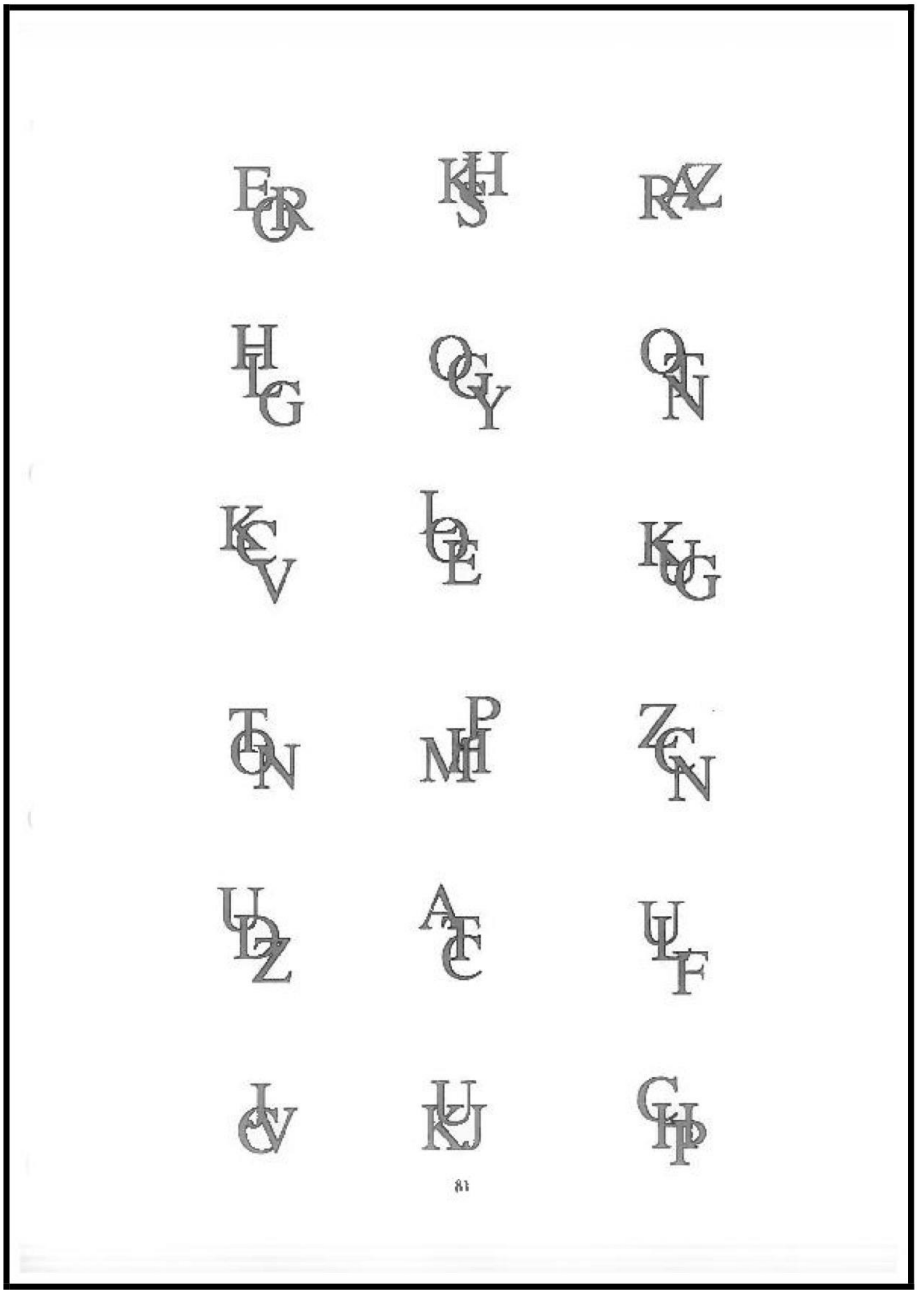
BORB 6 – Letters Paired Overlapping



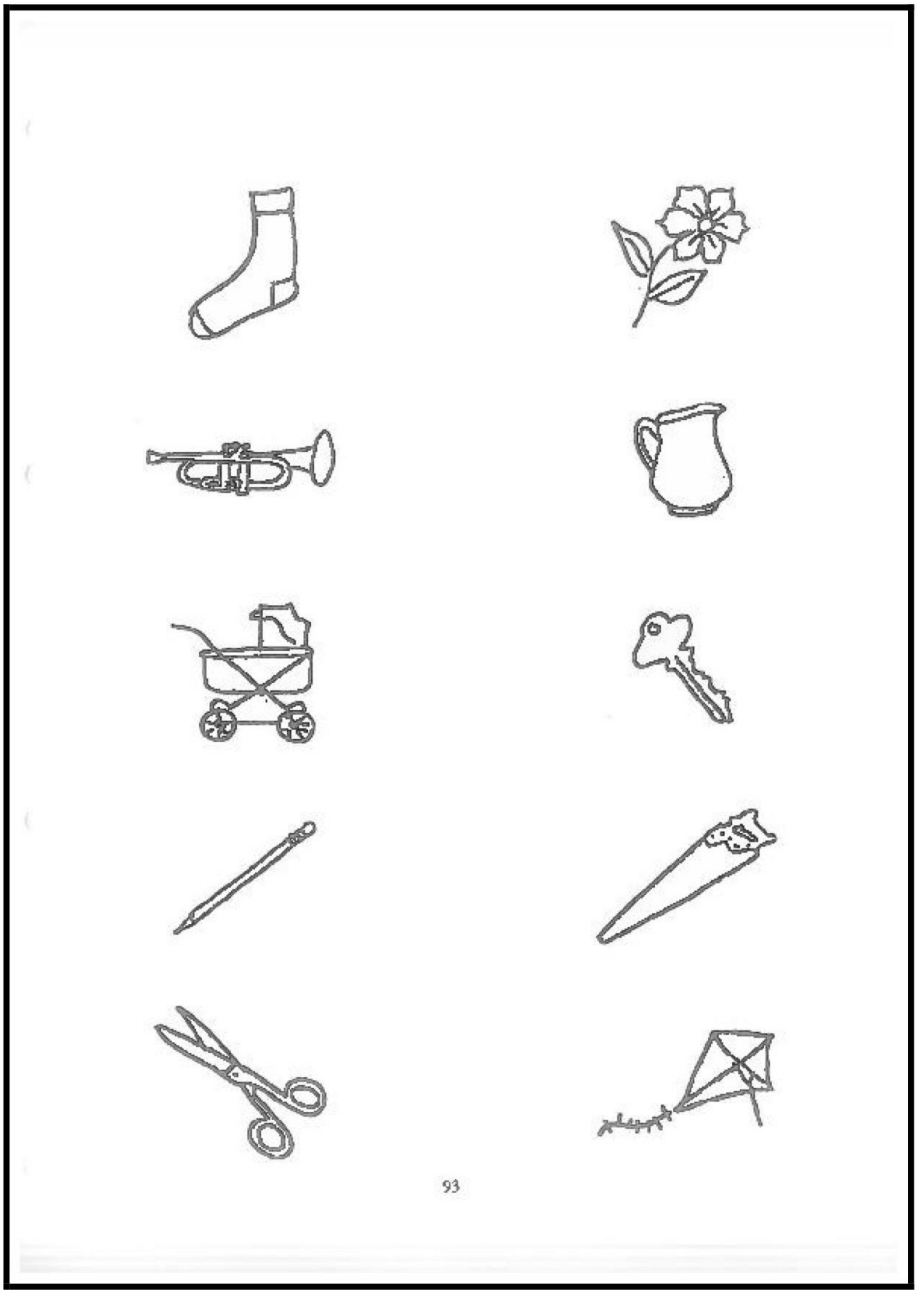
BORB 6 – Letters Triplets



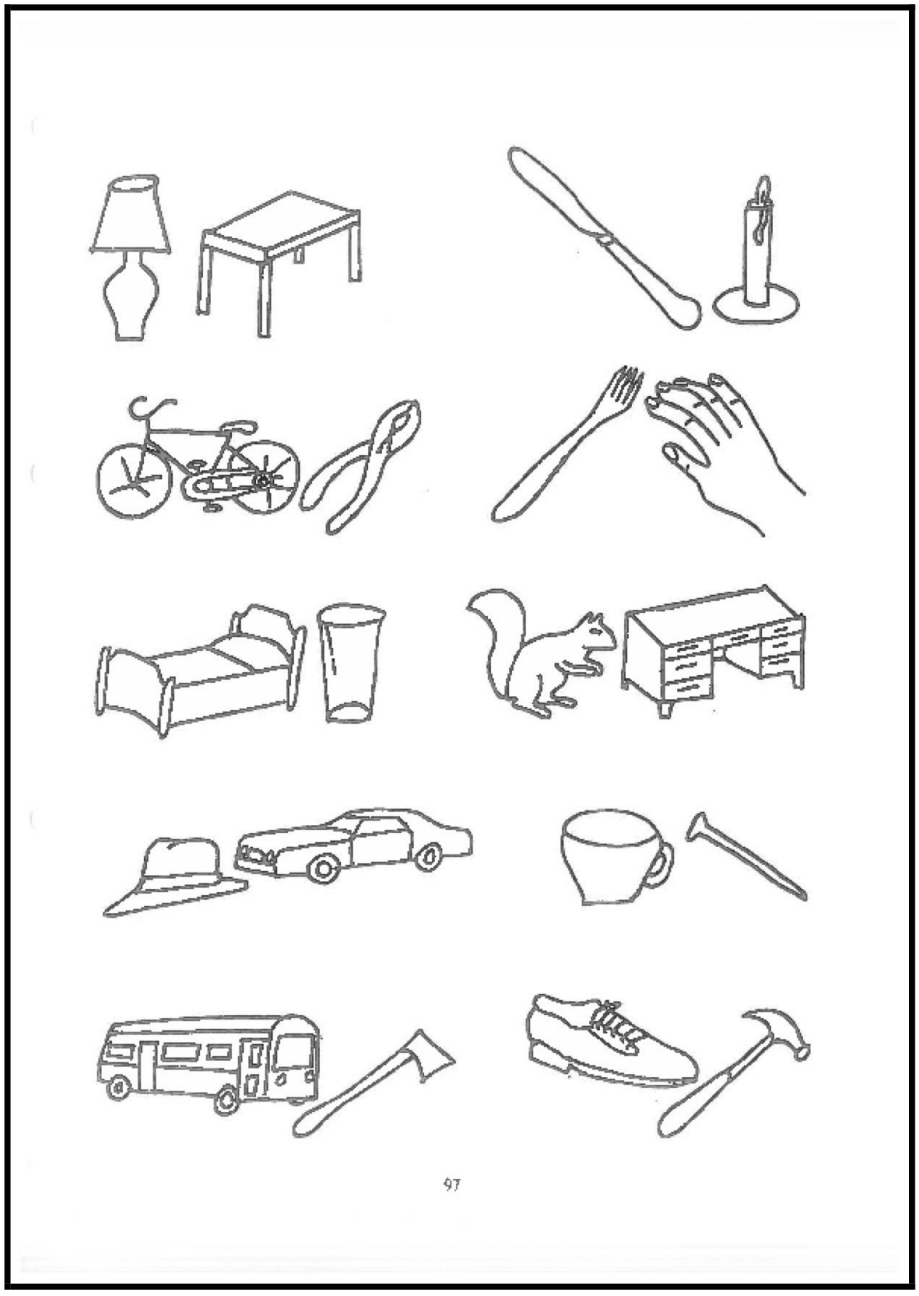
BORB 6 – Letters Triplets Overlapping



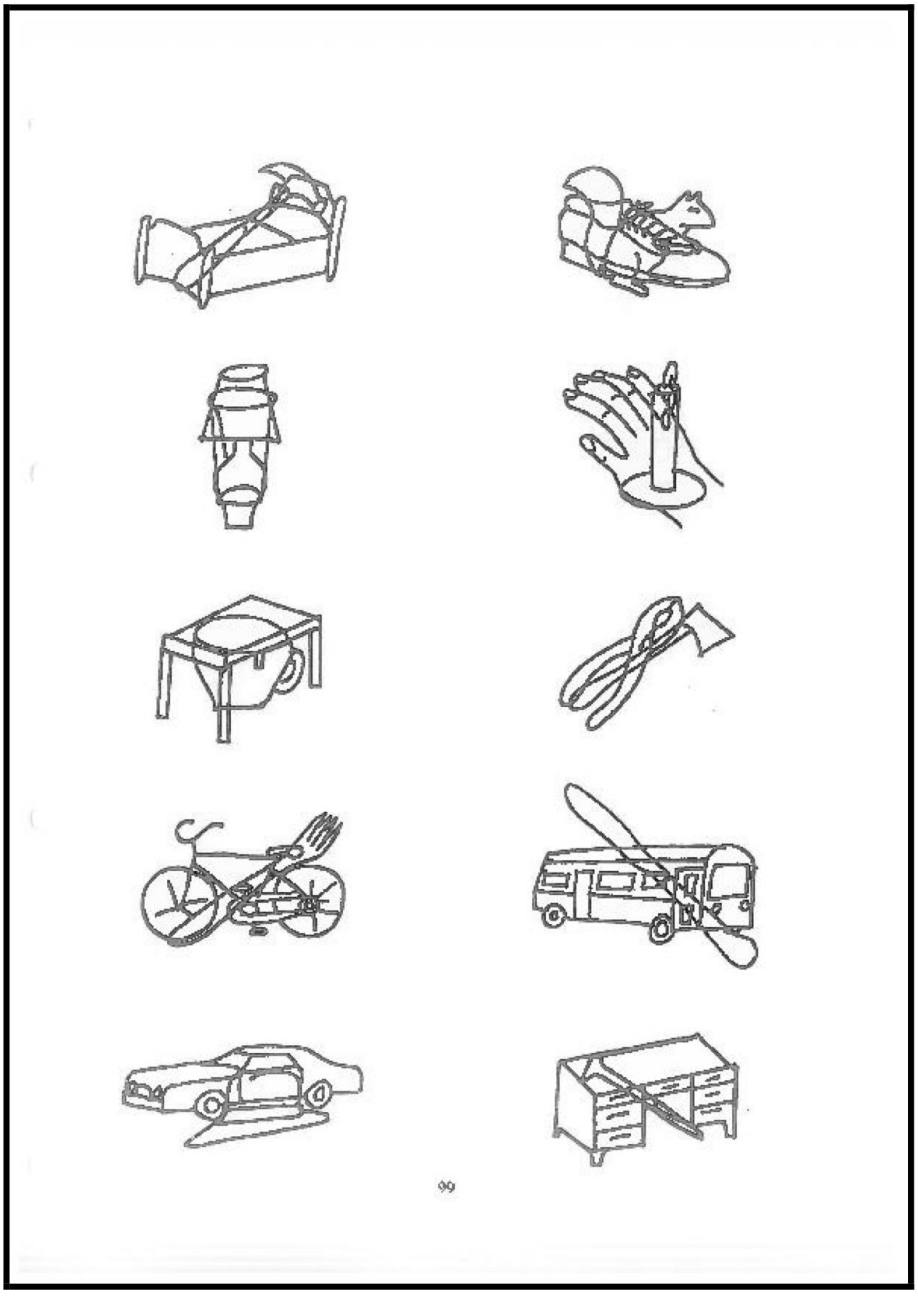
BORB 6 – Line Drawings Single

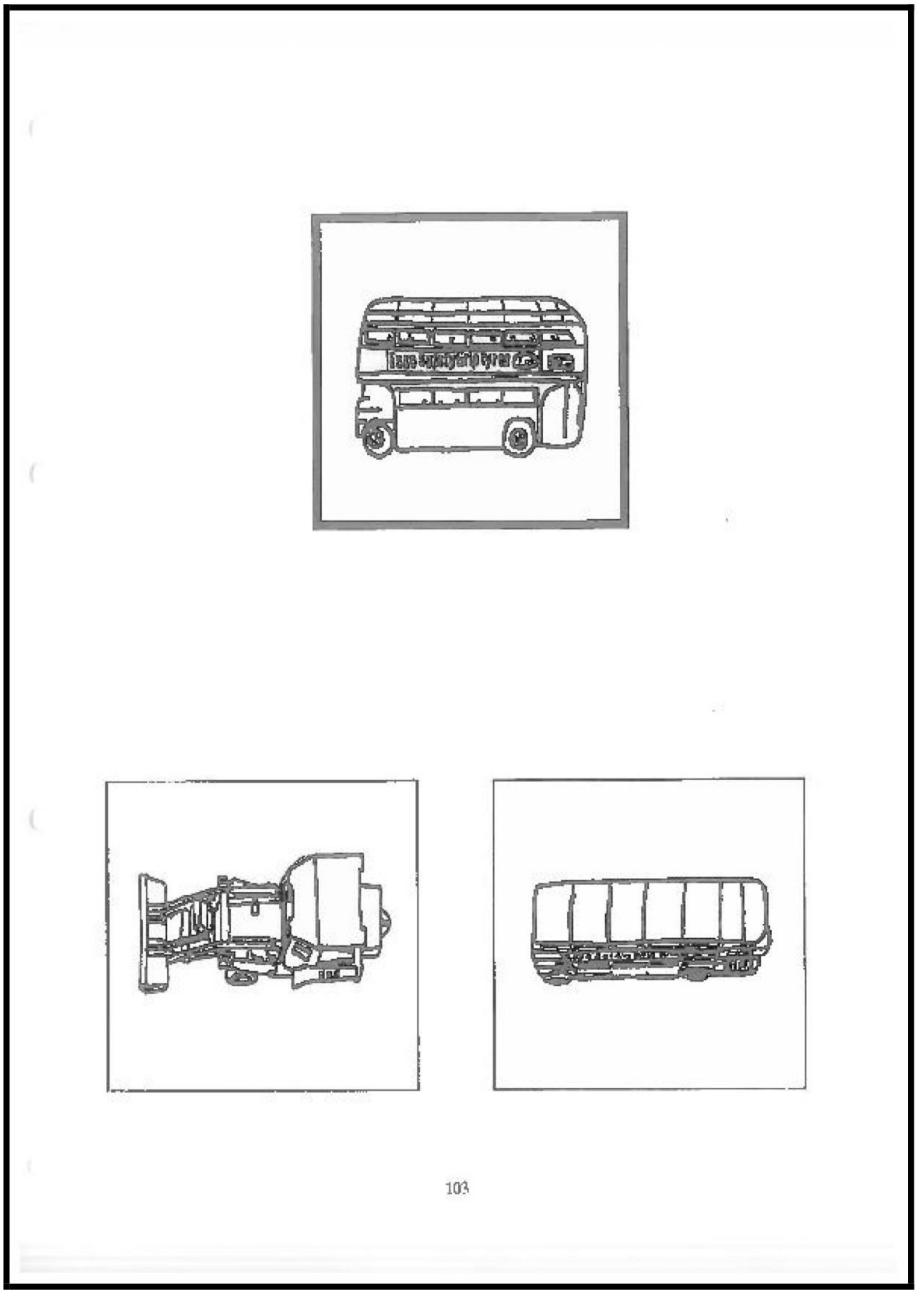


BORB 6 – Line Drawings Paired



BORB 6 – Line Drawings Paired Overlapping





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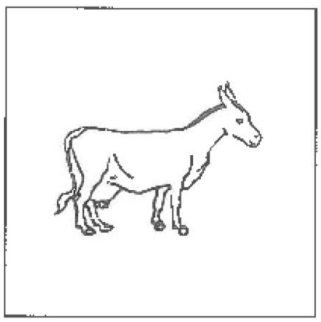
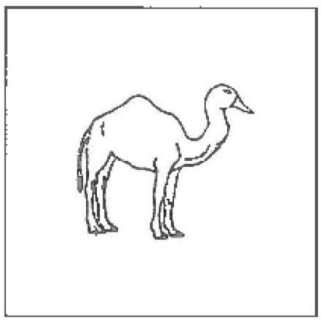
BORB 10A – Object Decision (Hard)

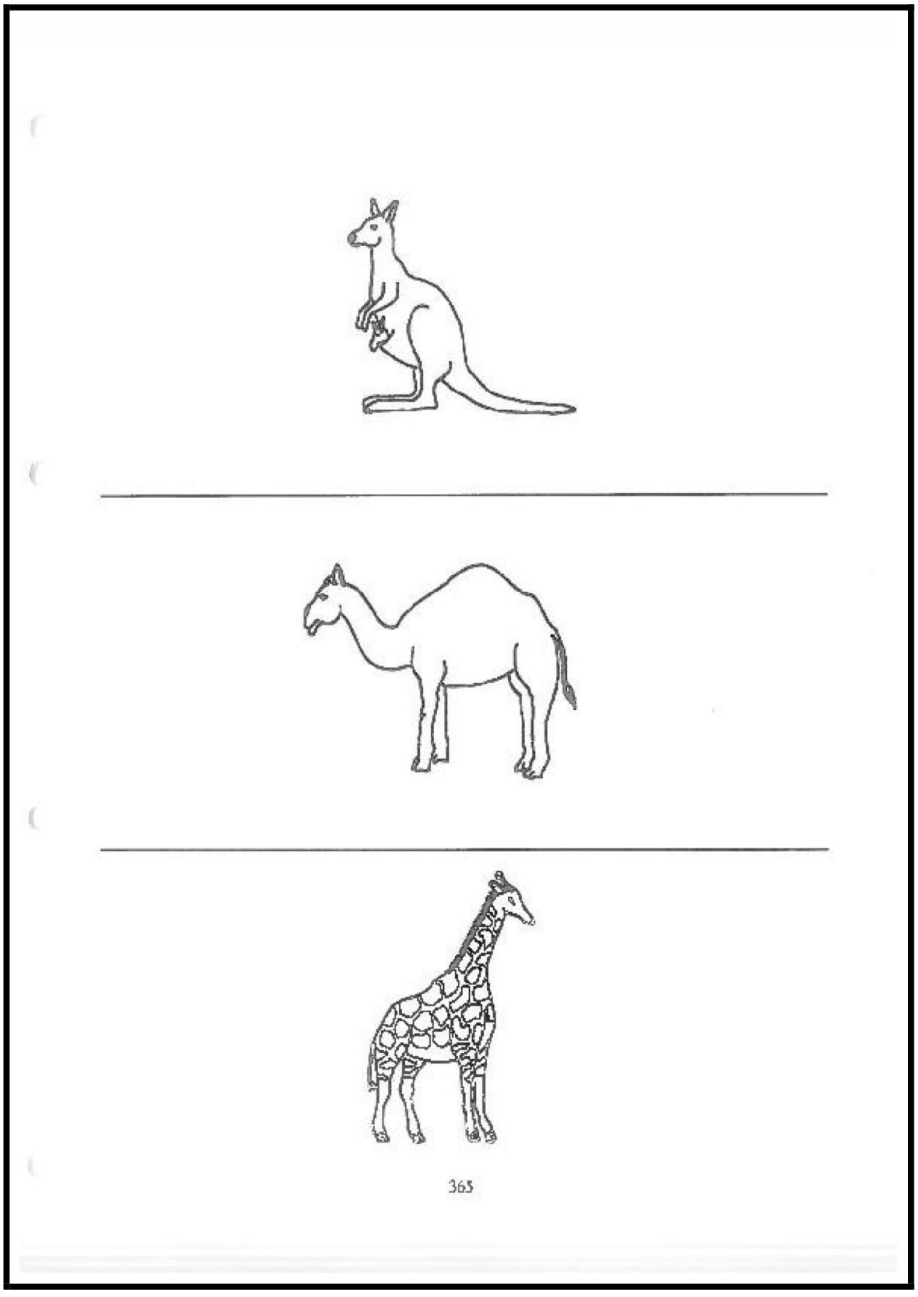


164

BORB 10B – Object Decision (Easy)



BORB 13 –Picture Naming (Short)



12.12 Appendix 12: TROG Example Page

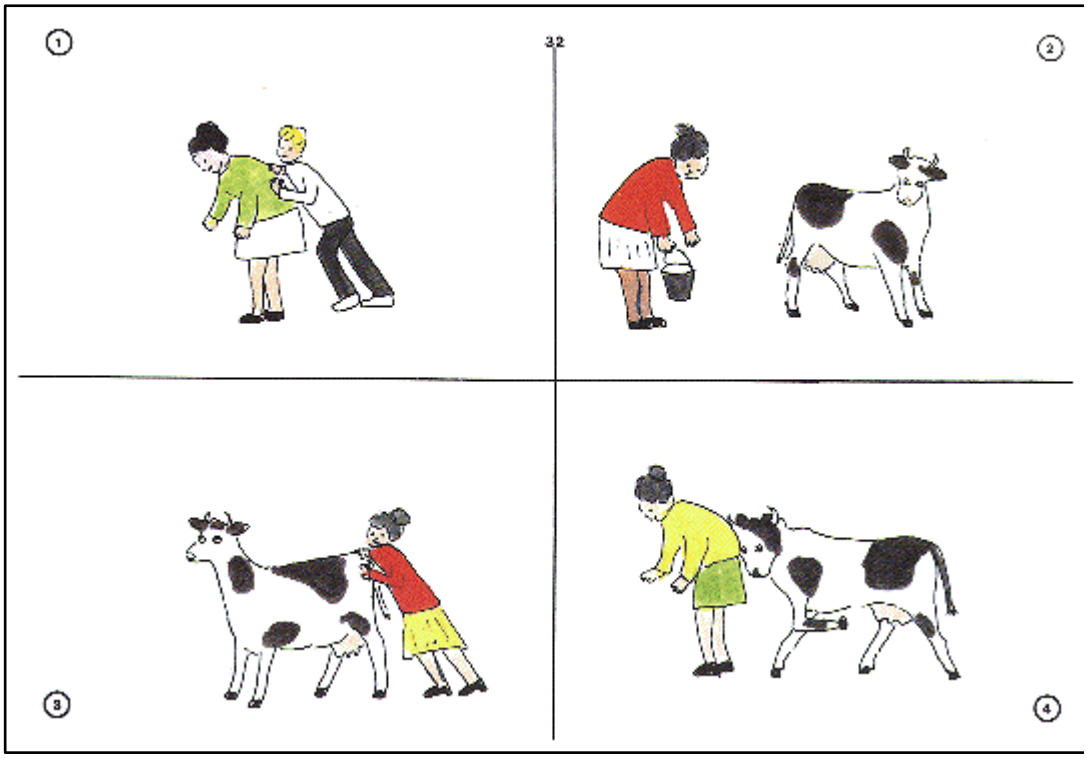


Figure 12.12.1: Example Stimulus Page from the TROG
For this example, the experimenter reads: "The cow is pushing the woman"
Note: The stimulus images were presented in A4 Landscape format and were scaled in size to fill the page.

12.13 Appendix 13: Alexia Passage

Author JK Rowling has told of her "excitement and dread" at writing the seventh and final Harry Potter book. Rowling admitted on her official website: "I can't quite imagine life without Harry."

Work on the follow-up to Harry Potter and the Half-Blood Prince will begin in January, she added."I contemplate the task with mingled feelings of excitement and dread, because I can't wait to get started," she wrote in a diary posting.

"I have been fine-tuning the fine-tuned plan for book seven during the past few weeks so I can really set to work in January." Rowling admitted: "Sometimes, even at this stage, you can see trouble looming; nearly all the six published books have had Chapters of Doom.

http://news.bbc.co.uk/1/hi/entertainment/4562536.stm accessed 4th October, 2015, 11.55AM.

12.14 Appendix 14: Group 4 and Group 5 Screening Phase Results

12.14.1 ACE-III

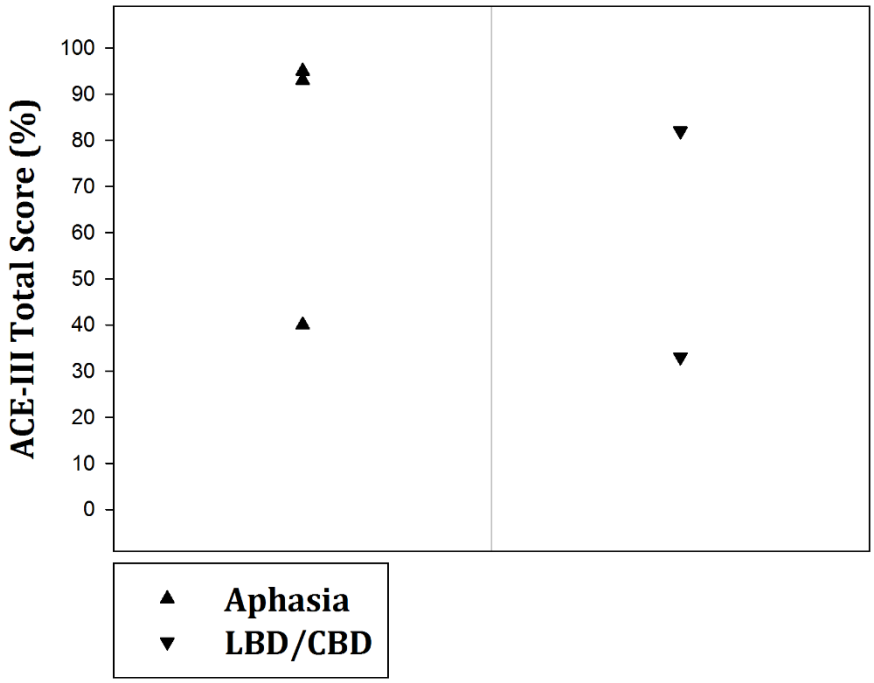


Figure 12.14.1.1: Boxplots Illustrating ACE-III Total Scores (percentage correct) for Group 4 and Group 5
Key: — — — represents control mean, · · · · · represents lower cut off for normal performance

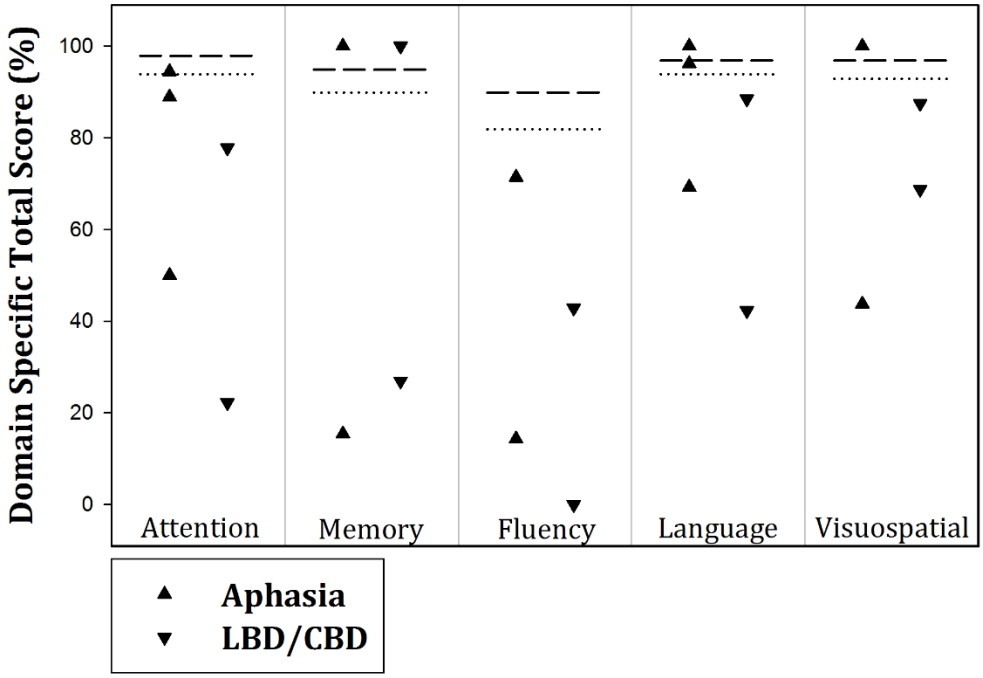


Figure 12.14.1.2: Scatterplot Illustrating Percentage Correct Score for Each Domain on ACE-III for All Patients in Group 4 and Group 5
Note: on the Memory, Fluency and Visuospatial subtests: two patients with Aphasia had equivalent performances, therefore these patients' symbols appear as one.
Key: — — — represents control mean, · · · · · represents lowest cut off for normal performance

	Aphasia			LBD/CBD		
	N	**A**	**NC**	**N**	**A**	**NC**
Attention	1	2	-	0	2	-
Memory	2	1	-	1	1	-
Fluency	0	3	-	0	2	-
Language	2	1	-	0	2	-
Visuospatial	2	1	-	0	2	-

Table 12.14.1.1: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on Each ACE-III Domain
Note: N = 'normal', greater than the level of lowest cut-off for healthy control performance. A = 'abnormal', below the level of lowest cut-off for healthy control performance, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest or for whom no data were available.

12.14.2 Memory

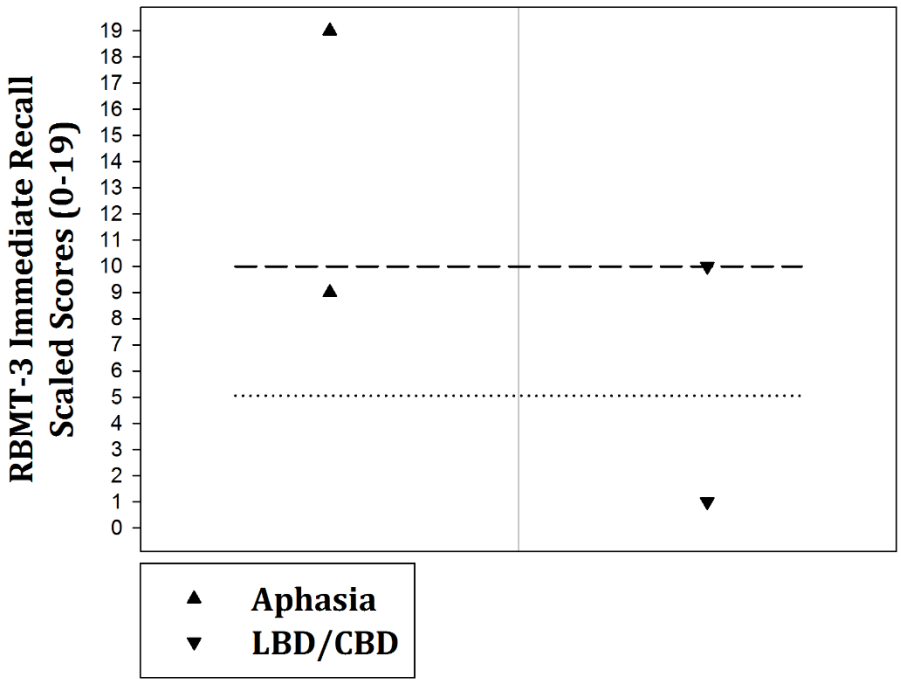


Figure 12.14.2.1: Scatterplot Illustrating Scaled RMBT-3 Immediate Recall Scores for All Patients in Group 4 and Group 5
Key: — — — represents control mean, · · · · · represents lowest cut off for normal performance

	Aphasia			LBD/CBD		
	N	**A**	**NC**	**N**	**A**	**NC**
RMBT-3 Immediate Recall	2	0	1	1	1	-

Table 12.14.2.1: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on the RMBT-3 Immediate Recall Subtest
Note: N = 'normal', greater than the level of lowest cut-off for healthy control performance. A = 'abnormal', below the level of lowest cut-off for healthy control performance, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.

12.14.3 Elementary visual features

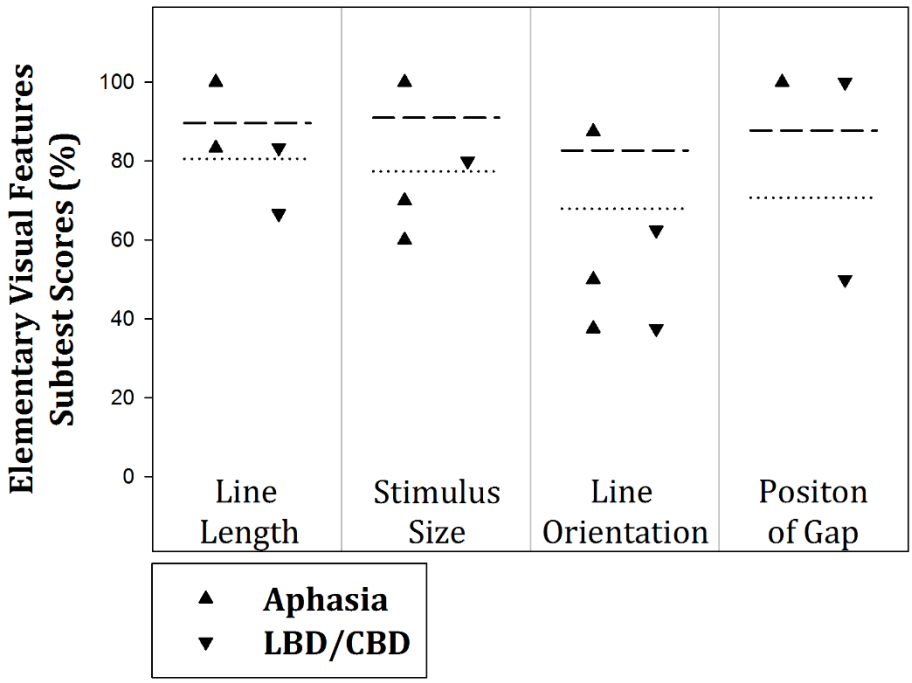


Figure 12.14.3.1: Scatterplot Illustrating Percentage Scores on Elementary Visual Features Subtests for All Patients in Group 4 and Group 5
Note: Line Length = BORB 2, Stimulus Size = BORB 3, Line Orientation = BORB 4, Position of Gap = BORB 5.
Key: — — — represents control mean, · · · · · represents lowest cut off for normal performance

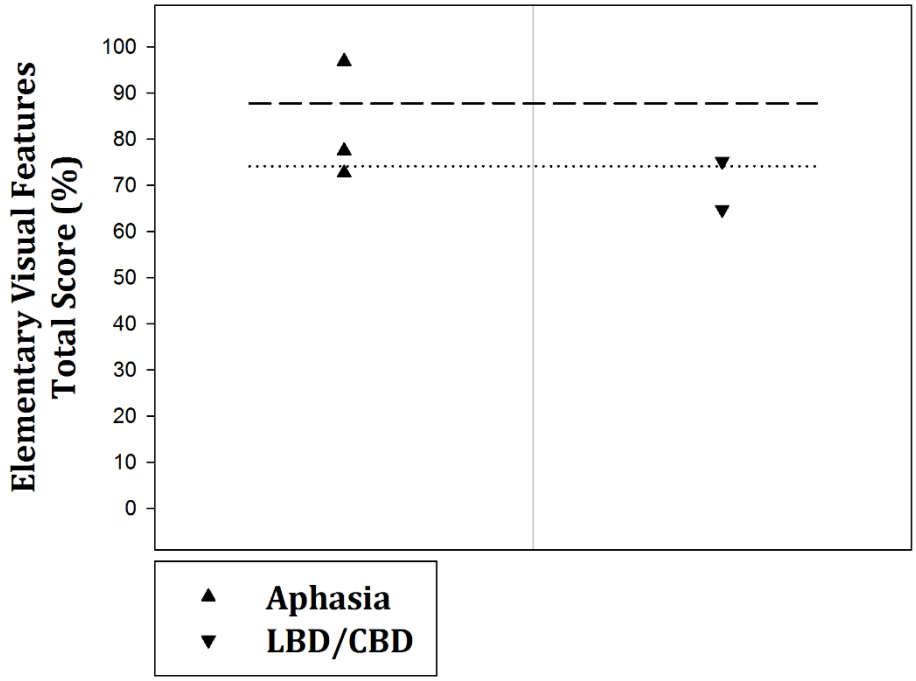


Figure 12.14.3.2: Scatterplot Illustrating Group Total Percentage Score on Elementary Visual Features Domain for Group 4 and Group 5
Key: — — — represents control mean, · · · · · represents lowest cut off for normal performance

	Aphasia			LBD/CBD		
	N	**A**	**NC**	**N**	**A**	**NC**
Elementary Visual Features Domain	2	1	-	1	1	-

Table 12.14.3.1: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on the Elementary Visual Features Domain
Note: N = 'normal', greater than the level of lowest cut-off for healthy control performance. A = 'abnormal', below the level of lowest cut-off for healthy control performance, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.

12.14.4 Perception of multiple figures

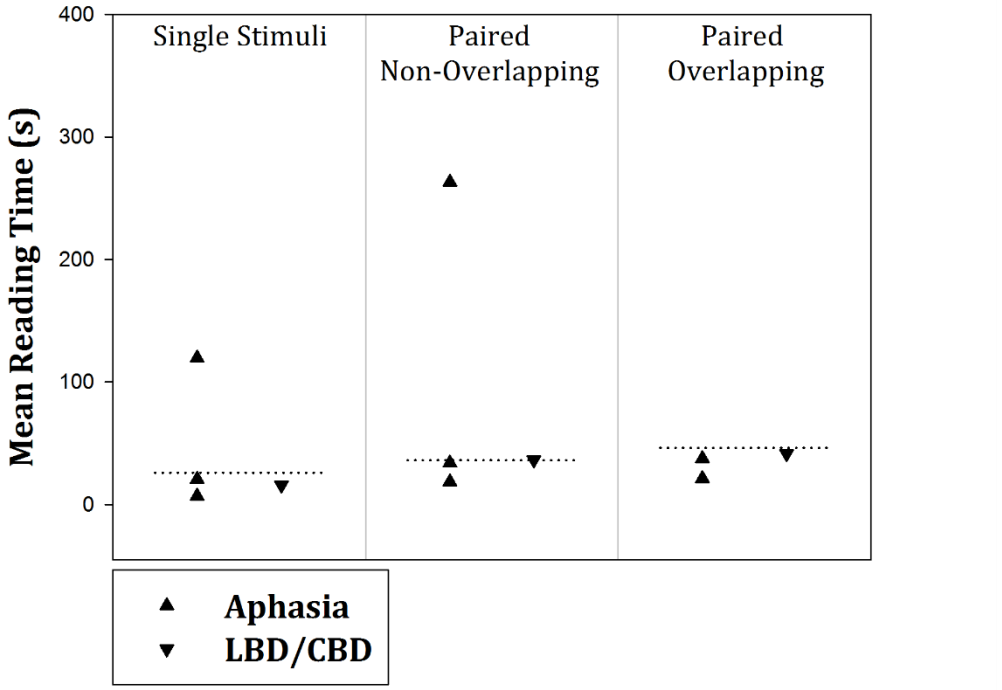


Figure 12.14.4.1: Scatterplot Illustrating Mean Reading Times (s) for Each Diagnostic Group Across Each Condition for Group 4 and Group 5
Key: · · · · · represents mean reading time across each condition for the worst control

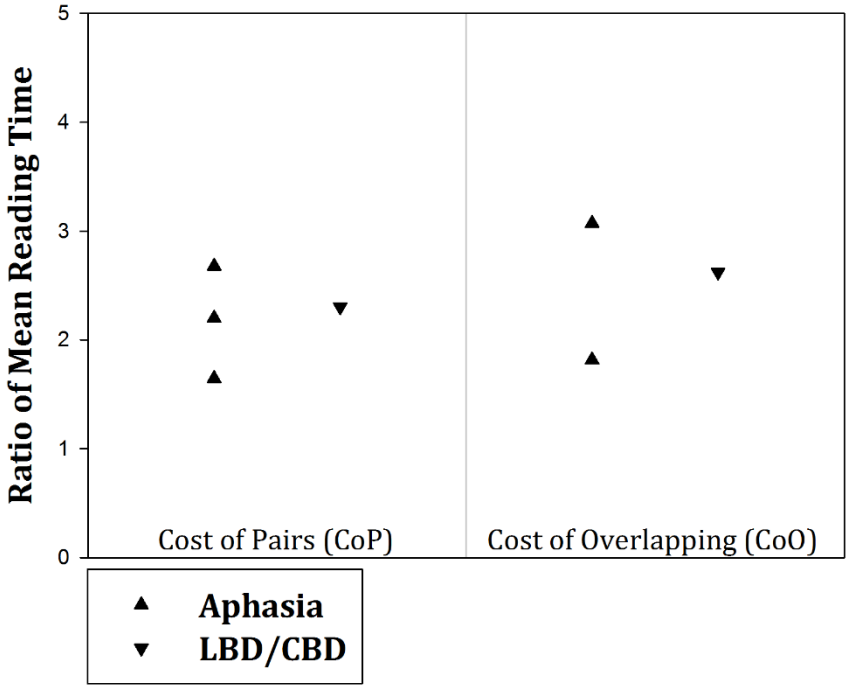


Figure 12.14.4.2: Scatterplots Illustrating Cost of Pairs (CoP) and Cost of Overlapping (CoO)* for Perception of Multiple Figures for Group 4 and Group 5

*Note: CoP and CoO are calculated as the ratio to the mean single stimuli reading time.

	Aphasia			LBD/CBD		
	N	**A**	**NC**	**N**	**A**	**NC**
Single Stimuli	2	1	-	1	0	-
Paired Non-Overlapping	2	1	-	0	1	-
Paired Overlapping	2	0	1	1	0	-

Table 12.14.4.1: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on Each Perception of Multiple Figures Subtest
Note: N = 'normal', greater than the level of lowest cut-off for healthy control performance. A = 'abnormal', below the level of lowest cut-off for healthy control performance. NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.
For this domain: the mean reading time from the worst control was used, and a mean reading time for each condition was calculated. This was used as the cut-off for coding performance. Patients who took longer than this cut off were coded as abnormal, those who took less time were coded as normal.

12.14.5 Object perception

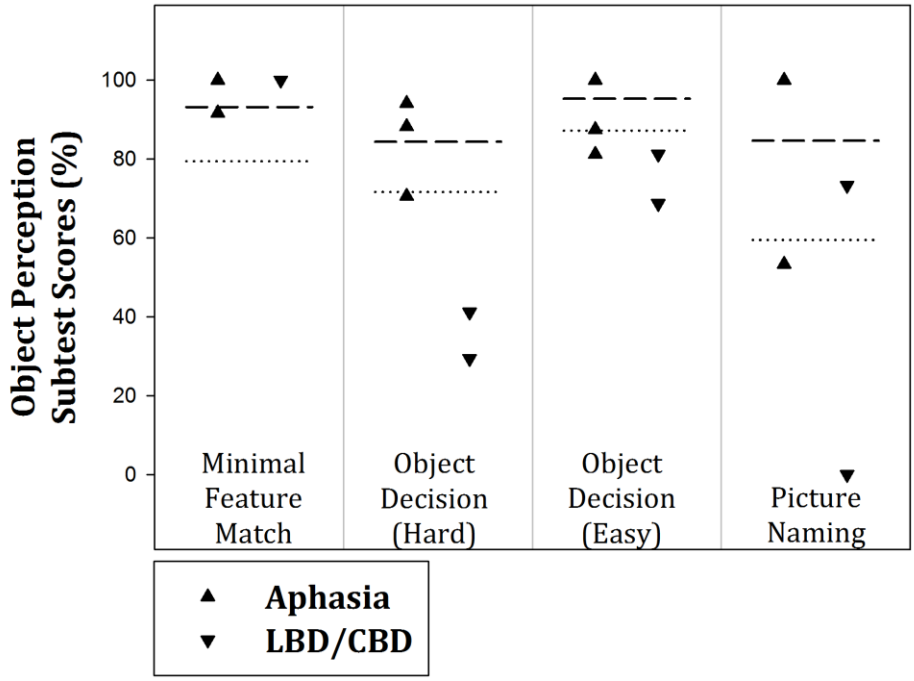


Figure 12.14.5.1: Scatterplot Illustrating Percentage Scores for Object Perception Subtests for Group 4 and Group 5
Note: Minimal Feature Match = BORB 7, Object Decision (Hard) = BORB 10A, Object Decision (Easy) = BORB 10B, Picture Naming = BORB 13.
Key: — — — represents control mean, · · · · · represents lowest cut off for normal performance

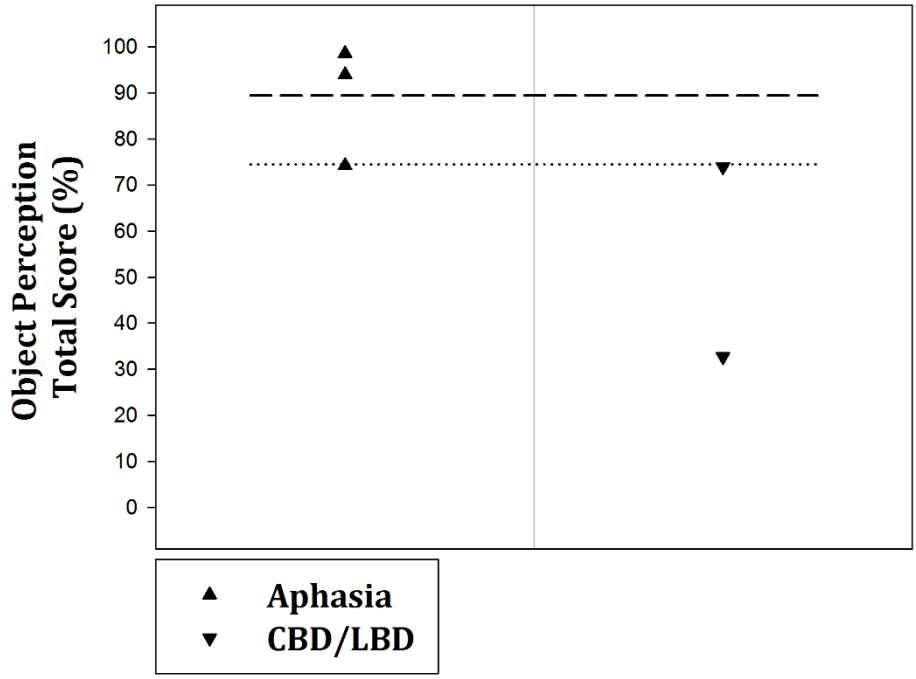


Figure 12.14.5.2: Scatterplot Illustrating Group Total Percentage Score on Object Perception Domain for Group 4 and Group 5
Key: — — — represents control mean, · · · · · represents lowest cut off for normal performance

	Aphasia			LBD/CBD		
	N	**A**	**NC**	**N**	**A**	**NC**
Object Perception Domain	2	1	-	0	2	-

Table 12.14.5.1: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on the Object Perception Domain
Note: N = 'normal', greater than the level of lowest cut-off for healthy control performance. A = 'abnormal', below the level of lowest cut-off for healthy control performance, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.

12.14.6 Constructional ability

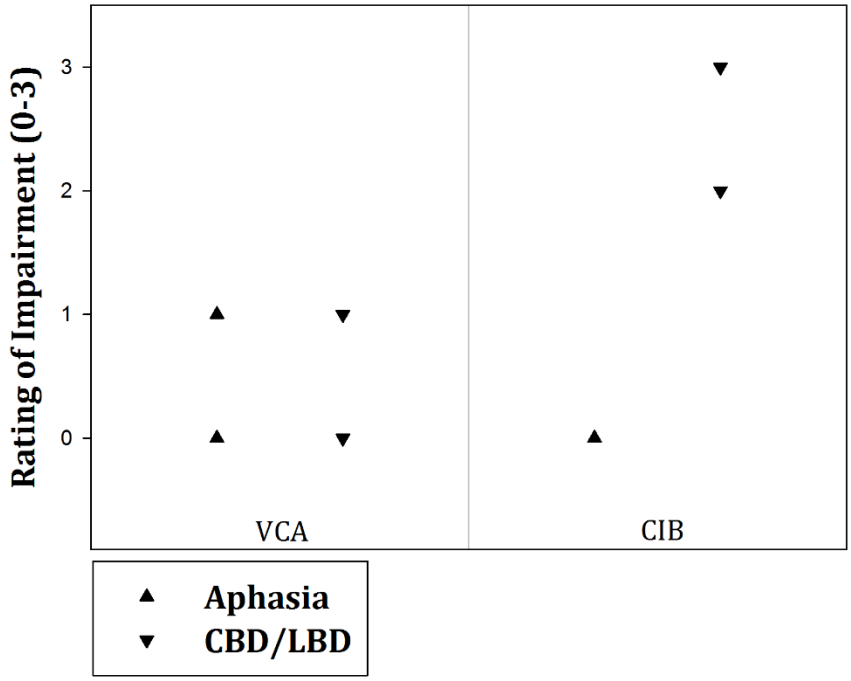


Figure 12.14.6.1: Scatterplot of M-LAST Performance Ratings for Patients on Visual Constructional Apraxia (VCA) and Closing-in Behaviour (CIB) for Group 4 and Group 5.

	Aphasia			LBD/CBD		
Severity	**VCA**	**CIB**	**NC**	**VCA**	**CIB**	**NC**
0	2	3		1	0	
1	1	0		1	0	
2	0	0		0	1	
3	0	0		0	1	
			-			-

Table 12.14.6.1: Frequency of Severity of Impairment for VCA and CIB on the Constructional Ability Domain for Group 4 and Group 5
Note: NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.

12.14.7 Spatial attention

12.14.7.1 Line Bisection

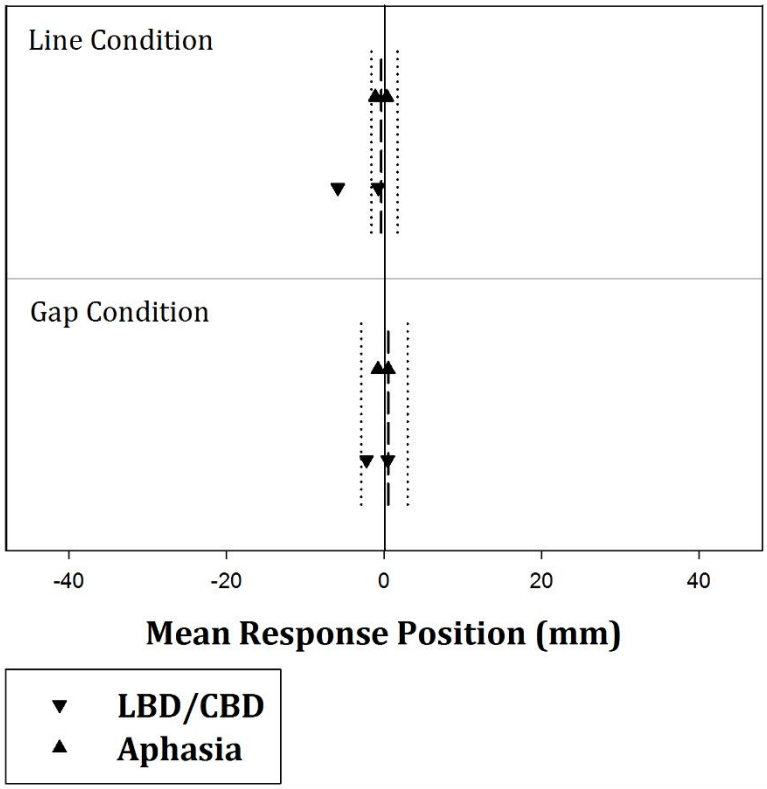


Figure 12.14.7.1.1: Scatterplot Illustrating Mean Response Position (mm) on Line Bisection Task for Group 4 and Group 5.
Note: Outliers are represented as black circles.
Key: — — — represents age- and sex-matched control mean response, · · · · · represents symmetrical boundaries of the cut off for normal performance.

	Aphasia			LBD/CBD		
	N	**A**	**NC**	**N**	**A**	**NC**
Line Condition	3	0		1	1	
Gap Condition	3	0		2	0	
			-			-

Table 12.14.7.1.1: Frequency of Severity of Impairment for VCA and CIB on the Constructional Ability Domain for Group 4 and Group 5
Note: N = 'normal', greater than the level of lowest cut-off for healthy control performance. A = 'abnormal', below the level of lowest cut-off for healthy control performance, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.
Note: NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.

12.14.7.2 Cancellation

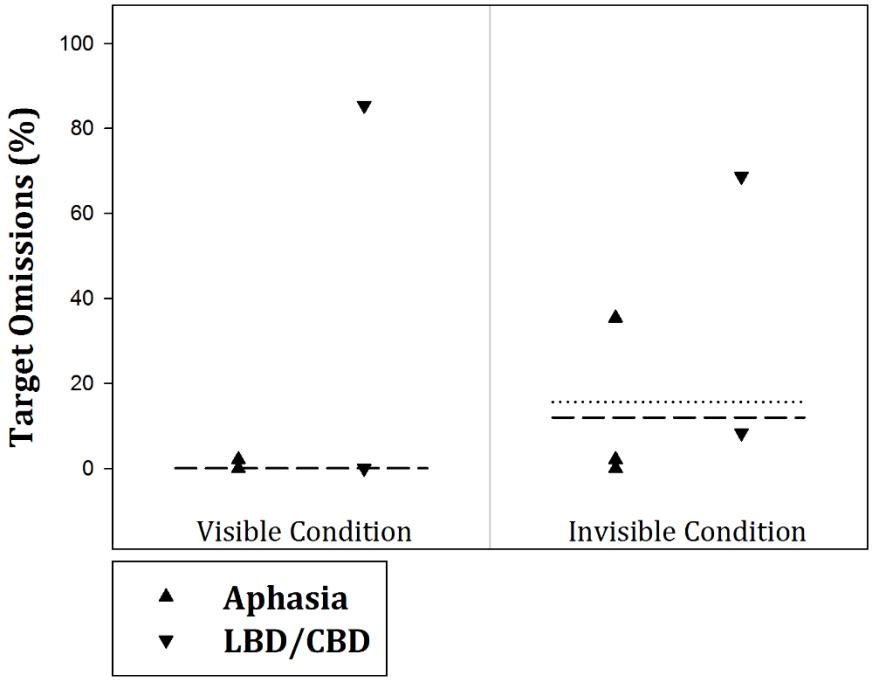


Figure 12.14.7.2.1: Scatterplot Illustrating Percentage of Target Omissions on Cancellation Task for Group 4 and Group 5.
Note: Outliers are represented as black circles.
Key: — — — represents age- and sex-matched control mean response, · · · · · represents lowest cut off for normal performance.
Note: All controls within the sample made 0 omissions in the visible condition, therefore no lowest cut off for normal performance could be calculated.

	Aphasia			LBD/CBD		
	N	**A**	**NC**	**N**	**A**	**NC**
Visible Condition	1	2		1	1	
Invisible Condition	2	1		1	1	
			-			-

Table 12.14.7.2.1: Frequency of Severity of Impairment for VCA and CIB on the Constructional Ability Domain for Group 4 and Group 5
Note: N = 'normal', greater than the level of lowest cut-off for healthy control performance. A = 'abnormal', below the level of lowest cut-off for healthy control performance, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.
Note: NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.

12.14.8 Executive control of attention

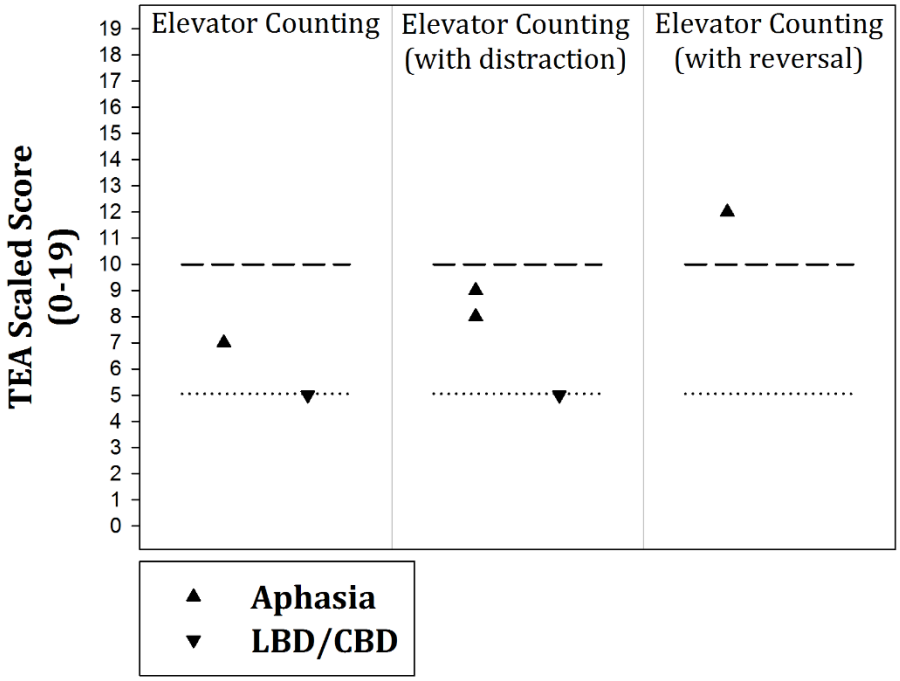


Figure 12.14.8.1: Scatterplot Illustrating Scaled TEA Scores for Group 4 and Group 5
Note: Outliers are represented as black circles.
Key: — — — represents control mean, · · · · · represents lowest cut off for normal performance

	Aphasia			LBD/CBD		
	N	**A**	**NC**	**N**	**A**	**NC**
Elevator Counting	2	0	1	0	1	1
Elevator Counting (with distraction)	2	0	1	0	1	1
Elevator Counting (with reversal)	1	0	2	-	-	2

Table 12.14.8.1: Frequency of Severity of Impairment for VCA and CIB on the Constructional Ability Domain for Group 4 and Group 5
Note: - is entered where no patients in this group completed the condition.
Note: N = 'normal', greater than the level of lowest cut-off for healthy control performance. A = 'abnormal', below the level of lowest cut-off for healthy control performance, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest
Note: Results from AD and FTD groups are presented for completeness, but are greyed out to indicate that these individual groups were not compared in further analysis.

12.14.9 Additional tests

12.14.9.1 Alexia

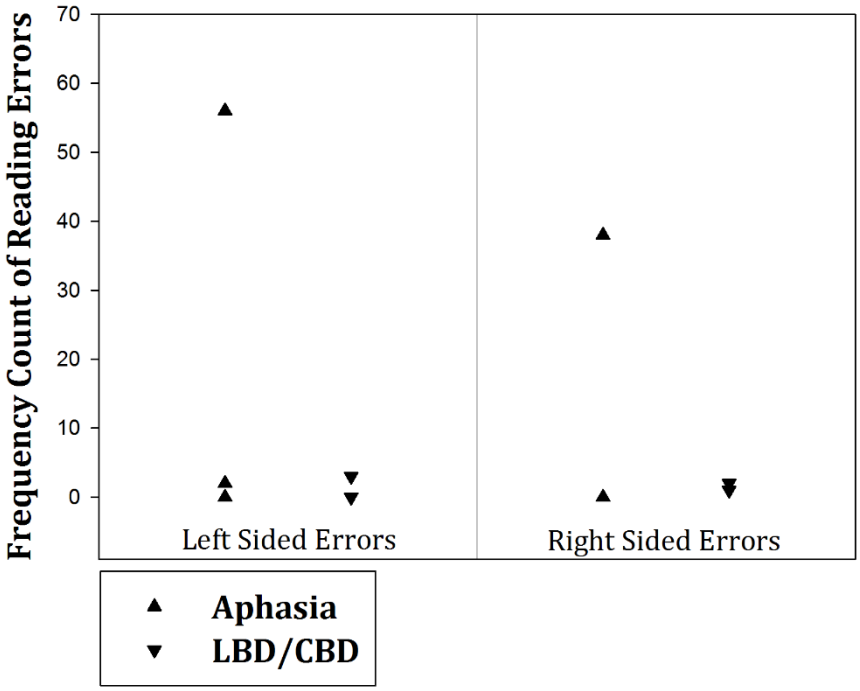


Figure 12.14.9.1.1: Scatterplot Illustrating Lateralisation of Reading Errors on Alexia Passage for Group 4 and Group 5

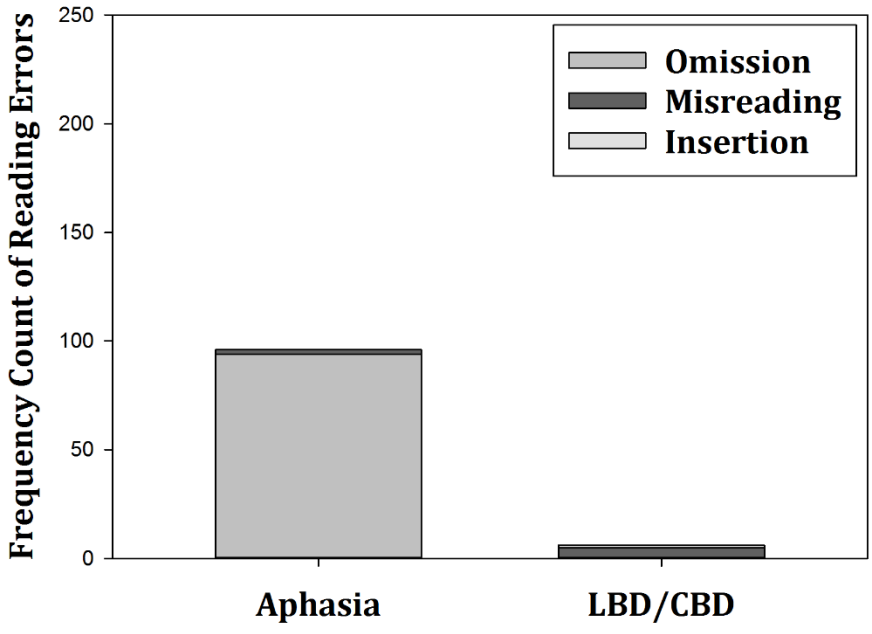


Figure 12.14.9.1.2: Boxplots Illustrating Rates of Different Error Types on Alexia Passage for Group 4 and Group 5

12.14.9.2 Finger Agnosia

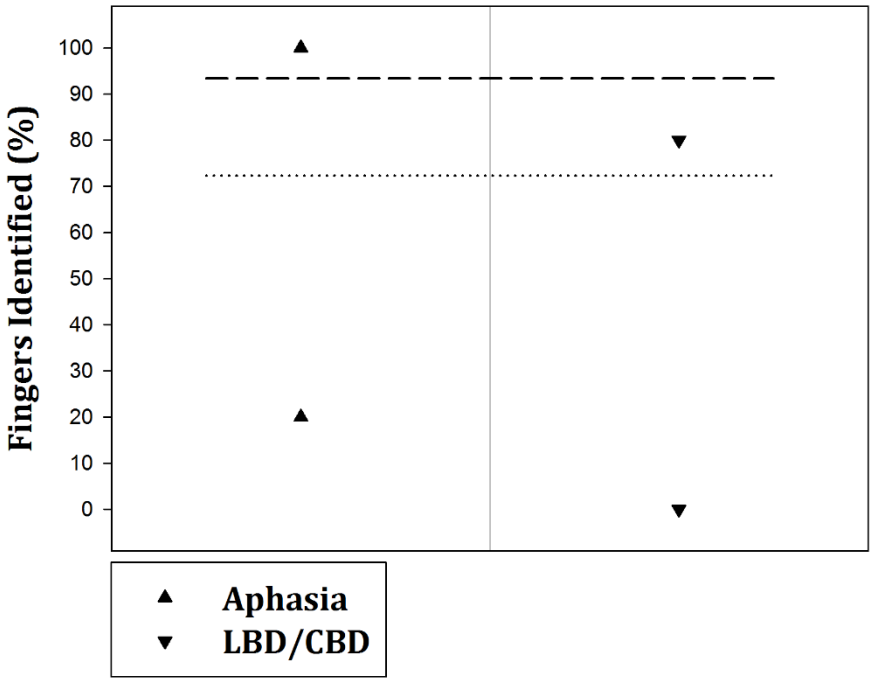


Figure 12.14.9.2.1: Scatterplot Illustrating Percentage of Fingers Identified for Group 4 and Group 5
Note: two patients with Aphasia had equivalent performances, therefore these patients' symbols appear as one.
Key: — — — represents age/sex matched control mean, · · · · · represents lowest cut off for normal performance

	Aphasia			LBD/CBD		
	N	**A**	**NC**	**N**	**A**	**NC**
Finger Agnosia	2	1	-	1	1	-

Table 12.14.9.2.1: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on the Object Perception Domain
Note: N = 'normal', greater than the level of lowest cut-off for healthy age/sex matched control performance. A = 'abnormal', below the level of lowest cut-off for healthy age/sex matched control performance, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest.
Note: Results from AD and FTD groups are presented for completeness, but are greyed out to indicate that these individual groups were not compared in further analysis.

12.14.9.3 TROG

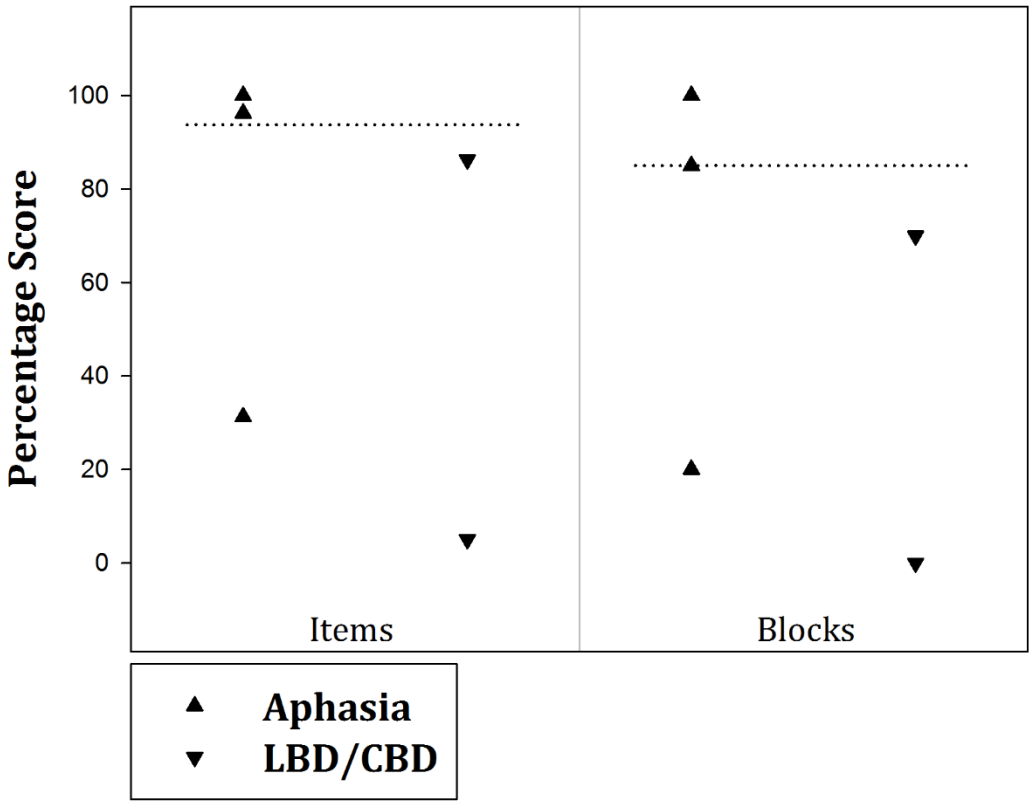


Figure 12.14.9.3.1: Scatterplot of Performance on the TROG at the Block and Item Level for Group 4 and Group 5
Key: · · · · · represents lowest cut off for normal performance, taken as the lowest value of the range reported in Croot, Hodges & Patterson, (1998).

	Aphasia			LBD/CBD		
	N	**A**	**NC**	**N**	**A**	**NC**
TROG Items	2	1		0	2	
TROG Blocks	2	1		0	2	
			-			-

Table 12.14.9.3.1: Frequency of Patients Performing Within Normal Control Limits, or Performing Abnormally on the Object Perception Domain
Note: N = 'normal', greater than the level of lowest cut-off for healthy control performance. A = 'abnormal', below the level of lowest cut-off for healthy control performance, NC = 'non-completers', indicating the number of patients within the full sample who did not complete the subtest. Cut-off taken as the lowest value of the range reported in Croot, Hodges & Patterson (1998).

12.15 Appendix 15: Optic Ataxia by Confrontation Response Form

HIT
CORRECTED ERROR
UNCORRECTED ERROR
MISS
NON-RESPONSE

OPTIC ATAXIA BY CONFRONTATION

Participant ID:
Date:

CONFRONTATION – FREE VISION

	RIGHT HAND	LEFT HAND
RIGHT VF		
LEFT VF		

CONFRONTATION – FIXATION

	RIGHT HAND	LEFT HAND
RIGHT VF		
LEFT VF		

12.16 Appendix 16: Extinction by Confrontation Response Form

EXTINCTION BY CONFRONTATION

Participant ID:
Date:

EXTINCTION

	Ss RIGHT SIDE	Ss LEFT SIDE	
UNILATERAL PRESENTATION	X		
		X	
		X	
	X		
		X	
	X		
	X		
		X	
	X		
		X	
	X		
		X	
BILATERAL PRESENTATION	X	X	B
	X	X	B
		X	L
	X		R
	X	X	B
	X	X	B
	X		R
		X	L
	X	X	B
	X	X	B
	X	X	B
		X	L
	X	X	B
	X		R
	X	X	B
	X	X	B

B = BILATERAL
L = LEFT
R = RIGHT